and observed for an additional period of up to 2 weeks. All high dose male mice were dead by the end of week 92. For each species, 50 animals of each sex were placed on test as controls and fed only the basal laboratory diet.

Mortality rates were dose-related for both sexes of both species. That incidences of certain tumors were higher in low dose than in high dose groups was probably due to accelerated mortality in the high dose group.

In dosed rats of both sexes, statistically significant incidences of bladder carcinomas (combined incidences of papillary carcinomas, squamous-cell carcinomas, transitional-cell papillomas, transitional-cell carcinomas, and undifferentiated carcinomas) and olfactory neuroblastomas were observed. The combined incidence of neoplastic nodules of the liver, hepatocelular carcinomas, or mixed hepato/cholangio carcinomas was also significant in low dose male rats.

In both male and female dosed mice, the incidence of bladder carcinomas (combined incidence of carcinomas NOS, squamous-cell carcinomas, and transitional carcinomas) was significant. The incidence of hepatocellular carcinomas was also significant in dosed female mice.

Under the conditions of this bioassay, p-cresidine was carcinogenic to Fischer 344 rats, causing increased incidences of carcinomas and of papillomas of the urinary bladder in both sexes, increased incidences of olfactory neuroblastomas in both sexes, and of liver tumors in males. p-Cresidine was also carcinogenic in $B6C3F_1$ mice, causing carcinomas of the urinary bladders in both sexes and hepatocellular carcinomas in females.

Synonyms: 2-methoxy-5-methylbenzeneamine; 2-methoxy- 5-methylaniline; 5-methyl-o-anisidine; m-amino-p-cresol methyl ether; MASO; cresidine

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Positive
Female Rats:	Positive
Male Mice:	Positive
Female Mice:	Positive

TR-143 Bioassay of 1,5-Naphthalenediamine for Possible Carcinogenicity (CAS No. 2243-62-1)

1,5-Naphthalenediamine, a bicyclic aromatic amine used in the dye industry, was selected for bioassay by the National Cancer Institute because of the high incidence of bladder cancer reported among dye manufacturing workers. Aromatic amines are one of a class of chemicals believed to contribute to the increased cancer risk in this industry.

A bioassay of 1,5-naphthalenediamine for possible carcinogenicity was conducted using Fischer 344 rats and $B6C3F_1$ mice. 1,5-Naphthalenediamine was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. The high and low dietary concentrations utilized in the chronic bioassay were, respectively, 0.1 and 0.05 percent for rats and 0.2 and 0.1 percent for mice. The compound was administered in the diet for 103 weeks, followed by up to 4 weeks of observation. Fifty mice of each sex and 25 rats of each sex were placed on test as controls. These animals were observed for up to 110 weeks.

There were no significant positive associations between the administered concentrations of 1,5-naphthalenediamine and mortality in either sex of rats or mice. In all groups adequate numbers of animals survived sufficiently long to be at risk from late-developing tumors.

Among dosed female rats, a statistically significant increase in endometrial stromal polyps was observed. Several of these tumors underwent malignant transformation to endometrial stromal sarcomas. The incidence of female rats having either adenoma or carcinoma of the clitoral gland was statistically significant. No neoplasms were observed at significantly increased incidences in dosed male rats. Based on lack of clinical signs or weight loss, the male rats may have been able to withstand a higher dose.

In mice, dose-related increases in thyroid neoplasms were observed in both sexes. The incidence of thyroid C-cell carcinomas was significant for high dose female mice. The combined incidences of papillary adenomas, follicular-cell adenomas and papillary cystadenomas of the thyroid were significant for mice of both sexes. The incidence of hepatocellular carcinomas and the incidence of alveolar/bronchiolar adenomas were each significant for dosed female mice.

Under the conditions of this bioassay, 1,5-naphthalenediamine was carcinogenic in female Fischer 344 rats, causing clitoral and uterine neoplasms. 1,5-Naphthalenediamine was also carcinogenic for $B6C3F_1$ mice, producing thyroid neoplasms in males and neoplasms of the thyroid, liver, and lung in females. Insufficient evidence was provided for the carcinogenicity of the compound in male Fischer 344 rats.

Synonym: 1,5-diaminonaphthalene

Report Date: 1978

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Positive
Male Mice:	Positive
Female Mice:	Positive

TR-144 Bioassay of 2-Aminoanthraquinone for Possible Carcinogenicity (CAS No. 117-79-3)

2-Aminoanthraquinone, an intermediate in the synthesis of anthraquinone dyes, was selected for bioassay by the National Cancer Institute in an attempt to determine which chemicals may be responsible for the

increased incidence of bladder cancer observed among workers in the dye manufacturing industry. Aromatic amines are one of several classes of chemicals thought to contribute to the increased cancer risk in this industry.

A bioassay of 2-aminoanthraquinone for possible carcinogenicity was conducted using Fischer 344 rats and $B6C3F_1$ mice. 2-Aminoanthraquinone was administered in the feed, at either of two concentrations (except for female rats), to groups of 50 male and 50 female animals of each species. The time-weighted average dietary concentrations used in the chronic bioassay were 0.69 and 0.35 percent for high and low dose male rats, respectively, 0.2 percent for the treated female rats, and 1.0 and 0.5 percent, respectively, for high and low dose mice of both sexes. After a 78-week period of chemical administration (80 weeks for high dose mice), observation of the rats continued for up to an additional 32, weeks and observation of the mice continued for up to an additional 16 weeks.

In both species adequate numbers of animals in all groups, except the treated female rats, survived sufficiently long to be at risk from late-developing tumors. The survival among treated female rats was poor and, as a result, no conclusions could be made regarding the carcinogenicity of the compound in these animals.

When male rats having either hepatocellular carcinomas or neoplastic nodules of the liver were combined and the resulting tumor incidences were analyzed statistically, there was a significant positive association between dosage and the incidences of these combined neoplasms. Hepatocellular carcinomas were observed at significantly higher incidences when dosed mice were compared to controls. There was a significantly higher incidence of malignant hematopoietic lymphomas in high dose female mice when compared to controls.

Under the conditions of this bioassay, dietary administration of 2-aminoanthraquinone was carcinogenic in male Fischer 344 rats, causing a combination of hepatocellular carcinomas and neoplastic nodules of the liver. The compound was also carcinogenic in $B6C3F_1$ mice, causing hepatocellular carcinomas in both sexes and malignant hematopoietic lymphomas in females.

Synonyms: 2-amino-9,10-anthracenedione; AAQ

Report Date: 1978

Levels of Evidence of Carcinogenicity:

Male Rats:	Positive
Female Rats:	Inadequate Study
Male Mice:	Positive
Female Mice:	Positive

TR-145 Bioassay of 3-Chloro-p-Toluidine for Possible Carcinogenicity (CAS No. 95-74-9)

3-Chloro-p-toluidine, a dye intermediate and avicide, was selected for bioassay by the National Cancer Institute because of the increased incidence of bladder cancer observed among workers in the dye manufacturing industry. Aromatic amines, of which 3-chloro-p-toluidine is one example, are among several classes of chemicals believed to contribute to this increased cancer risk.

A bioassay for the possible carcinogenicity of 3-chloro-p-toluidine was conducted using Fischer 344 rats and $B6C3F_1$ mice. 3-Chloro-p-toluidine was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. Twenty animals of each sex and species were placed on test as controls. The time-weighted average dietary concentrations of 3-chloro-p-toluidine administered to rats of both sexes were 3,269 and 1,635 ppm for the high and low dose groups, respectively. The high and low dietary concentrations of 3-chloro-p-toluidine administered to mice were, respectively, 1,200 and 600 ppm for males and 600 and 300 ppm for females. The compound was administered in the diet for 78 weeks, followed by an observation period of 24 weeks for high dose male rats, 25 weeks for all other dosed rats, and 12 weeks for mice.

There were no significant positive associations between the concentrations of 3-chloro-p-toluidine administered and mortality in either species. Adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. Mean body weight depression, relative to controls, was observed in high dose rats and mice of both sexes, indicating that the concentrations administered to these animals may have approximated the maximum tolerated dosages. The unusual incidences of nonneoplastic spleen and liver lesions in high dose rats supports this assumption.

Under the conditions of this bioassay there was no convincing evidence for the carcinogenicity of 3-chloro-p-toluidine in Fischer 344 rats or $B6C3F_1$ mice.

Synonyms: 3-chloro-4-methylbenzeneamine; 1-amino-3-chloro-4-methylbenzene; CPT

Report Date: 1978

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative
Male Mice:	Negative
Female Mice:	Negative

TR-146 Bioassay of Nithiazide for Possible Carcinogenicity (CAS No. 139-94-6)

Nithiazide, an antiprotozal compound used in veterinary medicine, was selected for bioassay by the National Cancer Institute because of its use and possible persistence in the tissues and eggs of animals raised for human consumption.

The bioassay of nithiazide for possible carcinogenicity was conducted using Fischer 344 rats and $B6C3F_1$ mice. Nithiazide was administered in the diet, at either of two concentrations, to groups of 50 male and 50 female animals of each species. The high and low concentrations of nithiazide utilized were, respectively, 1,250 and 625 ppm for rats and 5,000 and 2,500 ppm for mice. Dosed rats received feed containing nithiazide for 38 weeks, and as a result of a shortage of nithiazide, the animals were not fed the dosed feed for the next 9 weeks. The dosed feed diet was then resumed and continued for 56 weeks, after which time a 1-week observation period followed. Dosed mice received feed containing nithiazide for 61 weeks and, due to a shortage of nithiazide, the animals were not fed dosed feed for the next 9 weeks. The dosed feed diet was then resumed and continued for 33 weeks, followed by a 1-week observation period. Twenty animals of each sex and species were placed on test as controls.

In both species, adequate numbers of animals survived sufficiently long to be at risk from late-developing tumors. There was no significant positive association between dosage and mortality for either rats or mice. Compound-related mean body weight depression occurred in both sexes of each species.

Statistically significant incidences of hepatocellular adenomas and carcinomas were found in high dose male mice but not in female mice. Although the increased incidences of these tumors in dosed female mice were not statistically significant, the evidence presented was strongly suggestive of carcinogenicity to the liver in female $B6C3F_1$ mice. Statistically significant increased incidences of a combination of mammary and skin fibroadenomas and cystadenomas NOS were found in the high dose female rats. No unusual tumors were observed in either species.

Under the conditions of this bioassay, nithiazide was carcinogenic in male and probably female $B6C3F_1$ mice, causing a combination of hepatocellular carcinomas and hepatocellular adenomas. Nithiazide was also carcinogenic in female Fischer 344 rats, causing an increase in the incidence of mammary neoplasms. The compound was not carcinogenic in male Fischer 344 rats.

Synonyms: N-ethyl-N'-(5-nitro-2-thiazolyl) urea; 1-ethyl-3-(5-nitro-2-thiazolyl) urea

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Positive
Male Mice:	Positive
Female Mice:	Equivocal

TR-147 Bioassay of Mexacarbate for Possible Carcinogenicity (CAS No. 315-18-4)

Mexacarbate is one of a group of agricultural pesticides that scientists at the National Cancer Institute noted, in the late 1960's, had not been adequately tested for carcinogenicity. Mexacarbate has been used as an insecticide and as a molluscicide for the control of pests on lawns, turf, and flowers.

A bioassay of technical-grade mexacarbate for possible carcinogenicity was conducted using Osborne-Mendel rats and $B6C3F_1$ mice. Mexacarbate was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. The time-weighted average high and low dietary concentrations of mexacarbate were 418 and 209 ppm for male rats, 678 and 339 ppm for female rats, 654 and 327 ppm for male mice and 135 and 68 ppm for female mice. After a 78-week period of chemical administration, observation of rats continued for an additional 33 to 34 weeks and observation of mice continued for 14 to 15 additional weeks. For each species, 20 animals of each sex were placed on test as controls.

All groups except the male control mice survived sufficiently long to be at risk from late-appearing tumors. Because of poor survival of the male control mice, a pooled control group was used for statistical analysis of tumor incidence in male mice.

The possibility that female mice in this study did not receive maximum tolerated dosages of mexacarbate should be considered. Administration of mexacarbate had no significant effect on survival or body weights of female mice.

No neoplasms occurred in statistically significant increased incidences when dosed rats were compared to controls.

Among male mice surviving at least 56 weeks, significant associations with dietary concentrations were indicated by the Cochran-Armitage test for hepatocellular carcinomas, for subcutaneous fibrosarcomas and for fibromas of the skin. In none of these cases, however, were these results supported by significant Fisher exact tests.

Under the conditions of this bioassay, sufficient evidence was not obtained for the carcinogenicity of mexacarbate for Osborne-Mendel rats or $B6C3F_1$ mice.

Synonyms: 4-(dimethylamino)-3,5-dimethylphenyl methylcarbamate; 4-dimethylamino-3,5-xylyl methylcarbamate

Report Date: 1978

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative
Male Mice:	Negative
Female Mice:	Negative

TR-148 Bioassay of 1-Phenyl-2-thiourea for Possible Carcinogenicity (CAS No. 103-85-5)

1-Phenyl-2-thiourea was selected for bioassay by the National Cancer Institute because of the structural sim-

ilarity of this compound to ethylene thiourea, a tumorigen in hybrid mice (C57BL/6 x C3H/Anf and C57BL/6 x AKR), and the widespread oral exposure to this compound when used in classroom demonstrations of genetic polymorphism in taste.

A bioassay of 1-phenyl-2-thiourea for possible carcinogenicity was conducted using Fischer 344 rats and $B6C3F_1$ mice. 1-Phenyl-2-thiourea was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. The high and low concentrations of 1-phenyl-2-thiourea utilized in the chronic bioassay were, respectively, 120 and 60 ppm for rats and 300 and 150 ppm for mice. Twenty animals of each species and sex were placed on test as controls. A 78-week period of chemical administration was followed by an additional observation period of 26 weeks for rats and 13 weeks for mice.

Adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. Distinct dose-related depression of mean body weight gain was observed in male and female mice when compared with their controls, but growth retardation was not observed in any dosed rat group. In addition, since no significant accelerated mortality or other toxic effects were associated with the dietary administration of 1-phenyl-2-thiourea to rats, it is possible that the compound was not administered to these animals at the maximum tolerated concentrations.

There were no tumors in either sex of rats or mice for which a significant positive association could be established between chemical administration and tumor incidence.

Under the conditions of this bioassay, 1-phenyl-2-thiourea was not carcinogenic to Fischer 344 rats or $B6C3F_1$ mice.

Synonyms: Phenylthiourea; Phenylthiocarbamide; 1-Phenylthiourea; N-Phenylthiourea; PTU

Report Date: 1978

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative
Male Mice:	Negative
Female Mice:	Negative

TR-149 Bioassay of N,N'-Diethylthiourea for Possible Carcinogenicity (CAS No. 105-55-5)

N,N'-Diethylthiourea, a corrosion inhibitor and accelerator in elastomer manufacture, was selected for bioassay by the National Cancer Institute because of the structural similarity of this compound to ethylene thiourea, a tumorigen in hybrid mice (C57BL/6 x C3H/Anf and C57BL/6 x AKR).

A bioassay for the possible carcinogenicity of N,N'-diethylthiourea was conducted using Fischer 344 rats and $B6C3F_1$ mice. N,N'-Diethylthiourea was administered in the feed, at either of two concentrations, to groups of 50 males and 50 females of each species. Twenty animals of each sex and species, except for 19 male mice, were placed on test as controls. The high and low dietary concentrations of N,N'-diethylthiourea were, respectively, 250 and 125 ppm for rats and 500 and 250 ppm for mice. The compound was administered in the diet for 103 weeks, followed by an observation period of 1 week for all dosed groups.

There were no significant positive associations between the dosages of N,N'-diethylthiourea administered and mortality in rats or mice of either sex. Adequate numbers of animals in all dose groups survived sufficiently long to be at risk from late-developing tumors. Compound-related mean body weight depression was apparent among dosed male and female mice when compared to their respective controls, indicating that the concentrations of N,N'-diethylthiourea administered to mice may have approximated the maximum tolerated dosages.

There were statistically significant elevated incidences of follicular-cell carcinomas of the thyroid in high dose male rats. In addition, there were statistically significant elevated incidences of a combination of thyroid follicular-cell carcinomas and follicular-cell adenomas in high dose male and female rats.

Under the conditions of this bioassay, N,N'-diethylthiourea was carcinogenic to Fischer 344 rats, causing follicular-cell carcinomas of the thyroid in males and follicular-cell neoplasms of the thyroid in females. There was no evidence for the carcinogenicity of the compound in $B6C3F_1$ mice.

Synonyms: 1,3-diethyl-2-thiourea; 1,3-diethylthiourea

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Positive
Female Rats:	Positive
Male Mice:	Negative
Female Mice:	Negative

TR-150 Bioassay of Butylated Hydroxytoluene (BHT) for Possible Carcinogenicity (CAS No. 128-37-0)

The phenolic antioxidant butylated hydroxytoluene (BHT) was patented in 1947 and received approval for use as a food additive and preservative by the Food and Drug Administration (FDA) in 1954. Since 1959, BHT has been generally recognized as safe (GRAS) for use in foods and is one of the most commonly used antioxidants in foods containing fats.

A bioassay of BHT for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and $B6C3F_1$ mice.

Groups of 50 rats and 50 mice of each sex were administered BHT at one of two doses, either 3,000 or 6,000 ppm; the rats for 105 weeks and the mice for 107 or 108 weeks. Matched controls consisted of 20 untreated rats and 20 untreated mice of each sex. All surviving animals were killed at the end of administration of the test chemical.

Mean body weights of the dosed rats and mice were lower than those of the corresponding controls and were dose related throughout most of the bioassay. Survival was not affected significantly in the dosed groups of rats or mice, and the survival was 60% or greater in all dosed or control groups of rats and mice of each sex at the end of the bioassay. Sufficient number of animals were at risk for the development of late-appearing tumors.

Alveolar/bronchiolar carcinomas or adenomas occurred in the female mice at a significant incidence in the low-dose group ($P = 0.009$) but not in the high dose group, and the incidences were not significantly dose related (control 1/20, low-dose 16/46, high-dose 7/50). Thus, these lung tumors in the female cannot clearly be related to the administration of the BHT. No tumors occurred in either male or female rats at incidences that were significantly higher in dosed groups than in corresponding control groups. Nonneoplastic lesions that may have been related to the administration of the test chemical included focal alveolar histiocytosis at increased incidences in the dosed female rats and various lesions of the liver at increased incidences in the dosed male mice.

It is concluded that under the conditions of this bioassay, BHT was not carcinogenic for F344 rats or $B6C3F_1$ mice.

Synonyms: 2,6-di-tert-butyl-p-cresol, BHT

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative
Male Mice:	Negative
Female Mice:	Negative

TR-151 Bioassay of Lead Dimethyldithiocarbamate for Possible Carcinogenicity (CAS No. 19010-66-3)

The lead salt of bis(dimethyldithiocarbamic) acid is used commercially as a rubber accelerator in applications involving natural rubber, and styrene-butadiene, isobutylene-isoprene, isoprene, and butadiene rubber. Dithiocarbamate accelerators are known as ultra accelerators due to their speed of reaction. They are used primarily in latexes and rubber cements.

A bioassay of technical-grade lead dimethyldithiocarbamate for possible carcinogenicity was conducted by administering the test chemical in feed to F344 (Fischer) rats and $B6C3F_1$ mice.

Groups of 50 rats of each sex and 50 mice of each sex were administered lead dimethyldithiocarbamate at one of two doses, either 25 or 50 ppm, for 104 or 105 weeks. Matched controls consisted of 20 untreated rats and 20 untreated mice of each sex. All surviving animals were killed at the end of the period of administration of the test chemical.

Mean body weights of the dosed male rats and female mice were slightly lower than those of the corresponding controls; mean body weights of the dosed female rats and male mice were essentially the same as those of the corresponding controls. Survival rats in both species were unaffected by administration of the test chemical. The lack of toxicity in both species suggests that a maximum tolerated dose level may not have been used. Therefore, the studies may not have been conducted using maximum sensitivity for the assessment of the possible carcinogenicity of lead dimethyldithiocarbamate.

No tumors occurred in the rats or mice of either sex at incidences that were significantly higher in the dosed groups than in the control groups.

It is concluded that under the conditions of this bioassay, lead dimethyldithiocarbamate was not carcinogenic for F344 rats or $B6C3F_1$ mice of either sex.

Synonym: ledate

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative
Male Mice:	Negative
Female Mice:	Negative

TR-152 Bioassay of Ethyl Tellurac for Possible Carcinogenicity (CAS No. 20941-65-5)

Ethyl tellurac is used in rubber processing where it functions to accelerate the rate of vulcanization or formation of sulfur bridges between rubber polymers that produces modulus or rigidity in the finished product.

A bioassay of technical-grade ethyl tellurac for possible carcinogenicity was conducted by administering the preparation in feed to F344 rats and $B6C3F_1$ mice.

Groups of 50 rats of each sex were administered ethyl tellurac at one of two doses, either 300 or 600 ppm for the males and either 150 or 300 ppm for the females, for 105 weeks. Matched controls consisted of 20 untreated rats of each sex. All surviving rats were killed at 105 weeks.

Groups of 50 mice of each sex were administered ethyl tellurac at one of two doses, initially either 2,500 or 5,000 ppm. Due to signs of toxicity in the dosed animals, these doses were reduced to 500 and 2,000 ppm, respectively, starting at week 41 for the males and at week 38 for the females. The reduced doses were maintained for 66 weeks for the males; for the females, the reduced doses

were raised after 3 weeks to 2,000 and 5,000 ppm, respectively, and maintained at these levels for 66 weeks. The time-weighted average doses for the males were either 1,255 or 3,132 ppm; for the females, either 2,132 or 4,915 ppm. Matched controls consisted of 20 untreated mice of each sex. All surviving mice were killed at 106 weeks.

Mean body weights of the dosed groups of rats or mice were lower than those of corresponding controls throughout most or all of the bioassay. No other clinical signs in the rats or mice were clearly related to administration of the test chemical. Survival of the rats and the mice was not affected by the chemical, and sufficient numbers of all groups were at risk for the development of late-appearing tumors.

In the male rats, mesotheliomas occurred at incidences that were dose related ($P = 0.012$); in direct comparisons, the incidences of the tumors in the individual dosed groups were not significantly higher than that in the control group (controls 0/20, low-dose 2/49, high-dose 8/50). However, the historical-control data at this laboratory indicate an incidence of 12/416 (2.9%) in male F344 rats compared with 8/50 (16%) in the male high-dose group in this study.

In the female rats, no tumors occurred at incidences that were related to administration of the test chemical.

In both male and female mice, adenomas of the lacrimal (harderian) gland of the eye occurred in the dosed groups, but not in the corresponding controls (males: controls 0/17; low-dose 16/46, high-dose 10/49; females: controls 0/20, low-dose 6/50, high-dose 5/49). The incidences in the dosed groups were not high enough to show statistically significant dose-related trends. However, in direct comparisons of dosed and control groups of male mice, the incidence was statistically significant in the low-dose males ($P = 0.003$). In female mice, direct comparisons of dosed and control groups indicated that the incidence of this tumor was not statistically significant.

It is concluded that under the conditions of this bioassay, ethyl tellurac was not carcinogenic for F344 rats or $B6C3F_1$ mice of either sex. The incidence of mesotheliomas in dosed male rats and the incidence of adenomas of the lacrimal (harderian) gland of the eye in dosed mice of either sex provided evidence which was suggestive but under the conditions of the bioassay insufficient to establish the carcinogenicity of ethyl tellurac in these animals.

Synonym: tellurium diethyldithiocarbamate

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Equivocal
Female Rats:	Negative
Male Mice:	Equivocal
Female Mice:	Equivocal

TR-153 Bioassay of *o*-Toluidine Hydrochloride for Possible Carcinogenicity (CAS No. 636-21-5)

o-Toluidine and its hydrochloride salt are dye intermediates used in the manufacture of a large number of textile dyes which include some of the azo, triarylmethane, sulfur, and indigoid compounds. In addition, there are numerous substituted *o*-toluidines that are used as dye intermediates. *o*-Toluidine also functions as a photographic dye, as a reagent in a clinical assay for glucose and hemoglobin, and as an antioxidant in the manufacture of rubber.

A bioassay of o-toluidine hydrochloride for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and $B6C3F_1$ mice.

Groups of 50 rats of each sex and 50 mice of each sex were administered *o*-toluidine hydrochloride at one of several doses, either 3,000 or 6,000 ppm for rats and either 1,000 or 3,000 ppm for the mice, for 101 to 104 weeks. Matched controls consisted of 20 untreated rats of each sex and 20 untreated mice of each sex. All surviving rats and mice were killed at the end of administration of the test chemical.

Mean body weights of dosed male and female rats and mice were lower than those of corresponding matched controls and were dose related. Mortalities of the male and female rats were dose related and were relatively high at the end of the bioassay. Mortalities of the male and female mice were not, however, significantly affected by administration of the test chemical.

In rats, the administration of the test chemical induced several types of sarcomas of the spleen and other organs in both males and females, mesotheliomas of the abdominal cavity or scrotum in males, and transitional-cell carcinomas of the urinary bladder in females. Administration of the *o*-toluidine hydrochloride also resulted in increased incidences of fibromas of the subcutaneous tissue in the males and fibroadenomas or adenomas of the mammary gland in females.

In mice, hemangiosarcomas were induced at various sites in males, and hepatocellular carcinomas or adenomas were induced in females.

Under the conditions of this bioassay, o-toluidine hydrochloride was carcinogenic in both male and female F344 rats and $B6C3F_1$ mice, producing a significant increased incidence of one or more types of neoplasms.

Synonym: 2-aminotoluene hydrochloride

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Positive
Female Rats:	Positive
Male Mice:	Positive
Female Mice:	Positive

TR-154 Bioassay of Azobenzene for Possible Carcinogenicity (CAS No. 103-33-3)

Azobenzene occurs as a by-product during the manufacture of benzidine. Benzidine is a widely used intermediate for the azo dyes and other organic chemicals and is a carcinogen. Azobenzene itself has no known uses as a dyestuff and is only produced in small quantities for research purposes.

A bioassay of azobenzene for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and $B6C3F_1$ mice.

Groups of 50 rats of each sex were administered azobenzene at one of two doses, either 200 or 400 ppm, for 105 or 106 weeks. Matched controls consisted of 20 untreated rats of each sex. All surviving rats were killed at the end of administration of the test chemical.

Groups of 50 male mice were administered azobenzene at one of two doses, either 200 or 400 ppm, for 105 weeks. Groups of 50 female mice were administered the test chemical at one of two doses, initially 400 or 800 ppm, for 38 weeks. Because of excessively lowered body weights in the dosed groups of the females, doses for the females were then reduced to 100 and 400 ppm, respectively, and administration at the lowered doses was continued for 67 or 68 weeks. The time-weighted average doses for the female mice were either 208 or 545 ppm. Matched controls consisted of 20 untreated mice of each sex. All surviving mice were killed at the end of administration of the test chemical.

Mean body weights of dosed rats and mice of each sex were lower than those of corresponding controls, and were generally dose related throughout the bioassay. Mortality was dose related in the male rats and the female mice, but was not significantly affected in either the female rats or the male mice. Survival was 70% or greater at week 90 on study in all dosed and control groups of each species and sex; thus, sufficient numbers of animals were at risk in all groups for the development of late-appearing tumors.

In rats, a large number of sarcomas, including fibrosarcomas, hemangiosarcomas, and osteosarcomas in both males and females and malignant hemangiopericytomas in females, occurred in the spleen and other abdominal organs at incidences that were dose related in each sex ($P<0.001$) and that in direct comparisons were significantly higher ($P<0.001$) in the high-dose groups of each sex than in the corresponding control groups (males: controls, 0/20, low-dose 6/49, high-dose 31/49; females: controls 0/20, low-dose 5/50, high-dose 21/50).

In mice, no tumors occurred in either males or females at incidences that were significantly higher in the dosed groups than in the corresponding control groups.

It is concluded that under the conditions of this bioassay, azobenzene was carcinogenic (sarcomagenic) for F344 rats, inducing various types of sarcomas in the spleen and other abdominal organs of both males and females. The test chemical was not carcinogenic for $B6C3F_1$ mice of either sex.

Synonyms: diphenyldiimide; azobenzide

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Positive
Female Rats:	Positive
Male Mice:	Negative
Female Mice:	Negative

TR-155 Bioassay of 2,4,6-Trichlorophenol for Possible Carcinogenicity (CAS No. 88-06-2)

2,4,6-Trichlorophenol is a germicidal agent that has been used to preserve wood and glue as well as to protect textiles against mildew. Production of this chemical (for sale as an end product) was discontinued in 1975 by Dow Chemical Company, the only manufacturer of 2,4,6-trichlorophenol in the United States, because of the high cost of removing toxic dioxin impurities. However, a small quantity (2,204 pounds) was imported for domestic use in 1976.

A bioassay of 2,4,6-trichlorophenol for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and $B6C3F_1$ mice.

Groups of 50 rats of each sex were administered 2,4,6-trichlorophenol at one of two doses, either 5,000 or 10,000 ppm, for 106 or 107 weeks. Matched controls consisted of 20 untreated rats of each sex. All surviving rats were killed at the end of administration of the test chemical.

Groups of 50 male mice were administered 2,4,6-trichlorophenol at one of two doses, either 5,000 or 10,000 for 105 weeks. Groups of 50 female mice were administered the test chemical at one of two doses, initially either 10,000 or 20,000 ppm, for 38 weeks. Because of excessively lowered body weights in the dosed groups of the females, the doses for the females were then reduced to 2,500 and 5,000 ppm, respectively, and administration at the lower doses was continued for 67 weeks. The time-weighted average doses for the female mice were either 5,214 or 10,428 ppm. Matched controls consisted of 20 untreated mice of each sex. All surviving mice were killed at the end of administration of the test chemical.

Mean body weights of dosed rats and mice of each sex were lower than those of corresponding controls and were dose related throughout the bioassay. Survivals to the end of the experiment were 68% or greater in all groups of rats and 80% or greater in all groups of mice.

In the male rats, lymphomas or leukemias occurred at incidences that were dose related ($P = 0.006$) and in direct comparisons were significantly higher in the low-dose ($P = 0.019$) and high-dose ($P = 0.004$) groups than in the corresponding control group (controls 4/20; low-dose 25/50; high-dose 29/50). Leukocytosis and monocytosis of the peripheral blood and hyperplasia of the bone marrow also occurred in some dosed male rats not having lymphoma or leukemia.

In female rats, monocytic leukemia did not occur at incidences that were significant. However, as in the male rats, leukocytosis and monocytosis of the peripheral blood and hyperplasia of the bone marrow occurred in the dosed female rats but not in the controls (blood leukocytosis and monocytosis: controls 0/20, low-dose 6/50, high-dose 3/50; bone marrow hyperplasia: controls 0/20, low-dose 16/50, high-dose 2/50).

In both the male and female mice, hepatocellular carcinomas or adenomas occurred at incidences that were dose related ($P<0.001$), and in direct comparisons were significantly higher in the low- and high-dose male groups and the high-dose female group ($P \leq 0.001$) than in the corresponding control groups (males: controls 4/20, low-dose 32/49, high-dose 39/47; females: controls 1/20, low-dose 12/50, high-dose 24/48).

It is concluded that under the conditions of this bioassay, 2,4,6-trichlorophenol was carcinogenic in male F344 rats, inducing lymphomas or leukemias. The test chemical was also carcinogenic in both sexes of $B6C3F_1$ mice, inducing hepatocellular carcinomas or adenomas.

Synonyms: Omal®; Dowicide® 2S

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Positive
Female Rats:	Negative
Male Mice:	Positive
Female Mice:	Positive

TR-156 Bioassay of p,p'-Ethyl-DDD for Possible Carcinogenicity (CAS No. 72-56-0)

p,p'-Ethyl-DDD, an organochlorine insecticide which is marketed under the trade name Perthane®, has a lower toxicity to both insects and mammals than its structural analogs, DDT and DDD and is of moderate persistence in the environment. First marketed in 1950 for use against houseflies and cloth moths, it has since been used on vegetables, pears, and livestock. In the late 1950's, this compound was one of several DDT analogs that were administered to patients with breast or prostatic cancer for adrenocortical suppression because of the selective toxicity of these compounds for the adrenal cortex.

A bioassay of p,p'-ethyl-DDD for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and $B6C3F_1$ mice.

Groups of 50 rats of each sex were administered p,p'-ethyl-DDD at one of two doses, either 3,500 or 7,000 ppm, for 105 weeks. Matched controls consisted of 20 untreated rats of each sex. All surviving rats were killed at the end of administration of the test chemical.

Groups of 50 male mice were administered p,p'-ethyl-DDD at one of two doses, either 2,500 or 5,000 ppm, for 105 weeks. Groups of 50 female mice were administered the test chemical at one of two doses, initially either 5,000 or 10,000 ppm. Because of excessive lowered body weights in the dosed groups of females, the doses for the females were reduced after 48 weeks to 1,000 and 3,000 ppm, respectively, and administration at the lowered doses was continued for 57 weeks. The time-weighted average doses for the female mice were 2,828 and 6,200 ppm. Matched controls consisted of 20 untreated mice of each sex. All surviving mice were killed at the end of administration of the test chemical.

No tumors occurred in the male or female rats or in the male mice at incidences that could clearly be related to administration of the test chemical.

In female mice, hepatocellular carcinomas or adenomas occurred at incidences that were dose related ($P = 0.011$), but in direct comparisons the incidences in the individual dosed groups were not significantly higher than that in the corresponding control group. Although the occurrence of hepatocellular carcinomas or adenomas in the dosed female mice are not clearly related to the administration of the test chemical, the increased incidence of these tumors in the high-dose group suggests that the tumors may be related to the administration of p,p'-ethyl-DDD.

It is concluded that under the conditions of this bioassay, p,p'-ethyl-DDD was not carcinogenic for male or female F344 rats or male $B6C3F_1$ mice. However, the occurrence of hepatocellular carcinomas and adenomas in female mice was suggestive of a carcinogenic effect.

Synonym: 1,1-dichloro-2,2-bis(p-ethylphenyl)ethane

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative
Male Mice:	Negative
Female Mice:	Equivocal

TR-157 Bioassay of Methyl Parathion for Possible Carcinogenicity (CAS No. 298-00-0)

Methyl parathion is used in the agricultural industry as a contact and stomach poison with broad-spectrum insecticidal activity and some efficacy against mites. It is sold as a wettable power or emulsifiable concentrate for foliage application. Several formulations contain combinations of methyl parathion and ethyl parathion as well as other registered pesticides. There are 62 crops on which methyl parathion is registered for use, but over 90% of the total volume used in 1974 was on cotton. It is used to some extent in California for mosquito control.

A bioassay of methyl parathion for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and $B6C3F_1$ mice.

Groups of 50 rats of each sex were administered methyl parathion at one of two doses, initially either 62.5 or 125 ppm. These doses were maintained for 102 weeks

for the females; however, due to decreased mean body weight gain in the dosed males, the low and high doses for the males were reduced after 37 weeks to 20 and 50 ppm, respectively, and administration at the lowered doses was continued for 65 weeks. The time-weighted average doses for the male mice were 35 and 77 ppm, respectively, for the low- and high-dose groups. Matched controls consisted of 20 untreated mice of each sex. All surviving mice were killed at the end of administration of the test chemical.

Mean body weights of the dosed male and female rats and mice were lower than those of the corresponding controls throughout the bioassay and were dose related. Survival was unaffected in both species except for an increase in mortality in the high-dose female rats, in which 46% of the animals were alive at the end of the study.

No tumors occurred in any of the groups of rats or mice of either sex at incidences that were significantly higher in the dosed groups than in the corresponding control groups.

It is concluded that under the conditions of this bioassay, methyl parathion was not carcinogenic for F344 rats or B6C3F$_1$ mice of either sex.

Synonym: O,O-dimethyl O(4-nitrophenyl)-phosphorothioate

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative
Male Mice:	Negative
Female Mice:	Negative

TR-158 Bioassay of (2-Chloroethyl) trimethylammonium Chloride (CCC) for Possible Carcinogenicity (CAS No. 999-81-5)

(2-Chloroethyl)trimethylammonium chloride is a plant growth regulator, or dwarfing agent, used on poinsettias and azaleas in the United States, and on several food crops, specifically cereal grains, grapes, and pears in Europe.

A bioassay of (2-chloroethyl)trimethylammonium chloride for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and B6C3F$_1$ mice.

Groups of 50 rats of each sex were administered either 1,500 or 3,000 ppm of the compound for 108 weeks, and 50 mice of each sex were administered 500 or 2,000 ppm for 102 weeks. Matched controls consisted of 20 untreated and 20 untreated mice of each sex. All surviving animals were killed at the end of the period of administration of the test chemical.

Mean body weights of dosed rats and mice were lower than those of corresponding controls for part or all of the bioassay, except for the dosed male mice, whose mean body weights were essentially the same as those of the corresponding controls. Survival was not affected significantly in any of the dosed groups of rats or mice and was at least 64% in every dosed or control group of each species at the end of the bioassay. Sufficient numbers of dosed and control rats and mice of each sex were at risk for the development of late-appearing tumors. Since there was virtually no decrease in mean body weight in dosed male mice and only a slight decrease in female mice, and since there were no other toxic signs and no dose-related mortality, the animals may have been able to tolerate higher doses.

No tumors occurred in the rats or mice of either sex at incidences that could be associated with administration of the test chemical.

It is concluded that under the conditions of this bioassay, (2-chloroethyl)trimethylammonium chloride was not carcinogenic for F344 rats or B6C3F$_1$ mice of either sex.

Synonyms: Cyclocel®; chlormequat; chlorocholine chloride; CCC

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative
Male Mice:	Negative
Female Mice:	Negative

TR-159 Bioassay of Phthalic Anhydride for Possible Carcinogenicity (CAS No. 85-44-9)

Phthalic anhydride is an important chemical intermediate in the plastics industry. From it are derived numerous phthalate esters that function as plasticizers in synthetic resins. Phthalic anhydride itself is used as a monomer for synthetic resins such as glyptal, the alkyd resins, and the polyester resins. Phthalic anhydride is a precursor of anthraquinone, phthalein, rhodamine, phthalocyanine, fluorescein, and xanthene dyes. Reaction of phthalic anhydride with ammonia yields phthalimide, a useful reagent in the synthesis of primary amines, the agricultural fungicide phaltan, and thalidomide. Other reactions yield phenolphthalein, benzoic acid, phthalylsulfathiazole (an intestinal antimicrobial agent), and terephthalic acid.

A bioassay of phthalic anhydride for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and B6C3F$_1$ mice.

Groups of 50 rats of each sex were administered the test chemical at one of two doses, initially either 25,000 or 50,000 ppm, for 32 weeks. Because of excessive depres-

sions in the amount of body weight gained in the dosed groups, the doses for the males were then reduced to 12,500 and 25,000 ppm, respectively, and the doses for the females were reduced to 6,250 and 12,500 ppm. Administration of the test chemical at the lowered doses was continued for 72 weeks. The time-weighted average doses for the males were either 16,346 or 32,692 ppm, and those for the females were either 12,019 or 24,038 ppm. Matched controls consisted of 20 untreated mice of each sex. All surviving mice were killed at the end of the period of administration of the test chemical.

Mean body weights of the high-dose male rats and of the low- and high-dose mice of each sex were lower than those of the corresponding controls; mean body weights of the low-dose male rats and of both the low- and high-dose female rats were essentially unaffected by administration of the test chemical. Depressions in the amount of body weight gained in the male and female mice were dose related throughout the bioassay. Survivals of the rats and mice were not affected by administration of the test chemical.

No tumors occurred in the rats or mice of either sex at incidences that could be clearly related to the administration of the test chemical.

It is concluded that under the conditions of this bioassay, phthalic anhydride was not carcinogenic for F344 rats or B6C3F$_1$ mice of either sex.

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative
Male Mice:	Negative
Female Mice:	Negative

TR-160 Bioassay of 2,4,5-Trimethylaniline for Possible Carcinogenicity (CAS No. 137-17-7)

2,4,5-Trimethylaniline is a component of a mixture of aromatic amines used in the synthesis of the red dye Ponceau 3R. This dye is produced by diazotizing a mixture of amine intermediates, some of which have been identified as methyl-, dimethyl-, or trimethylanilines, and coupling them with 2-naphthol-3,6-disulfonic acid. Ponceau 3R is therefore a complex mixture containing some 1-(2,4,5-trimethylphenylazo)-2-naphthol-3,6-disulfonic acid.

Ponceau 3R has been used as a color additive in foods since 1907. It was certified as FD&C (Food Drug and Cosmetic) Red No. 1 from 1940 until 1960, at which time it was withdrawn from general use. Provisional recertification as Ext. D&C (External Drug and Cosmetic) Red No. 15 was granted shortly thereafter in 1961, but was revoked in 1968.

A bioassay of 2,4,5-trimethylaniline for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and B6C3F$_1$ mice.

Groups of 50 rats and 50 mice of each sex were administered 2,4,5-trimethylaniline at one of two doses, either 200 or 800 ppm for the rats and either 50 or 100 ppm for the mice, for 101 weeks. Matched controls consisted of 20 untreated rats and 20 untreated mice of each sex. All surviving animals were killed at the end of administration of the test chemical.

Mean body weights of the dosed male and female rats were generally lower than those of corresponding controls; mean body weights of the dosed mice were only slightly lower in the males than in the corresponding controls and were unaffected or affected irregularly in the females. Survival was not affected significantly when the rats or mice were administered the test chemical and was 70% or greater in all dosed or control groups. Sufficient numbers of animals were at risk for late-appearing tumors.

In the rats, hepatocellular carcinomas or neoplastic nodules occurred at incidences that were dose related in both males and females ($P \leq 0.001$), and in direct comparisons the incidences were slightly higher in the high-dose males, high-dose females, and low-dose females ($P \leq 0.004$) than in corresponding controls (males: controls 1/19; low-dose 6/50; high-dose 20/50; females: controls 0/20; low-dose 12/49, high-dose 27/50). In addition, alveolar/bronchiolar carcinomas or adenomas occurred in the female rats at incidences that were dose related ($P = 0.003$), and in a direct comparison the incidence was significantly higher in the high-dose group ($P = 0.017$) than in the corresponding control group (controls 0/20; low-dose 3/43; high-dose 11/50).

In the female mice, hepatocellular carcinomas occurred at incidences that were dose related ($P \leq 0.001$), and in direct comparisons the incidences were significantly higher ($P \leq 0.001$) in the low- and high-dose animals than in the corresponding controls (controls 0/20, low-dose 18/49, high-dose 40/50). Because historical records of this laboratory for control B6C3F$_1$ male mice show a relatively high incidence of hepatocellular carcinomas, an increased incidence of these tumors in 2,4,5-trimethylaniline dosed male mice as compared with matched controls could not be clearly associated with administration of the test compound.

It is concluded that under the conditions of this bioassay, 2,4,5-trimethylaniline was carcinogenic for male and female F344 rats and female B6C3F$_1$ mice, inducing hepatocellular carcinomas or neoplastic nodules in the rats of each sex, alveolar/bronchiolar carcinomas in the female rats, and hepatocellular carcinomas in female mice.

Synonym: pseudocumidine

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Positive
Female Rats:	Positive
Male Mice:	Equivocal
Female Mice:	Positive

TR-161 Bioassay of Phthalamide for Possible Carcinogenicity (CAS No. 88-96-0)

Phthalamide is recommended for use as an accelerator for curing epoxy resins. It is believed to be used chiefly in the paint industry.

A bioassay of phthalamide for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and $B6C3F_1$ mice.

Groups of 50 rats of each sex were administered phthalamide at one of two doses, either 15,000 or 30,000 ppm for the males and either 5,000 or 10,000 ppm for the females, for 106 weeks. Groups of 50 mice of each sex were administered the test chemical at one of two doses, 25,000 or 50,000 ppm for the males, and at one of three doses, 6,200, 12,500, or 25,000 ppm, for the females, for 103 or 105 weeks. Matched controls consisted of 20 untreated rats of each sex, 20 untreated male mice, and two groups of 20 untreated female mice. All surviving rats and mice were killed at the end of administration of the test chemical.

Mean body weights of the dosed groups of rats and mice were either slightly lower than those of corresponding control groups or essentially unaffected by administration of the test chemical. Also, survival was unaffected in the rats and mice except for early deaths in the high- and mid-dose groups of female mice. Survival was 66% or greater at the end of the bioassay in all dosed groups and control groups of each species and sex except for the high-dose group of female mice (36%). With the exception of the high-dose female mice, sufficient numbers of animals were at risk in all groups for the development of late-appearing tumors.

No tumors occurred in the rats or mice of either sex at incidences that were significantly higher in the dosed groups than in the corresponding control groups. However, phthalamide produced toxic lesions in the livers of male and female rats and the urinary systems of female rats and mice. The presence of nonneoplastic lesions suggests that the MTD may have been used or exceeded.

It is concluded that under the conditions of this bioassay, phthalamide was not carcinogenic for F344 rats or $B6C3F_1$ mice of either sex.

Synonyms: o-phthalic acid diamide; P-D

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative
Male Mice:	Negative
Female Mice:	Negative

TR-162 Bioassay of 2,4-Diaminotoluene for Possible Carcinogenicity (CAS No. 95-80-7)

2,4-Diaminotoluene is a widely used industrial intermediate. Most of this chemical produced in the United States is converted to toluene diisocyanate for use in the synthesis of polyurethanes. 2,4-Diaminotoluene is also an intermediate in the for the synthesis of dyes and used for textiles, fur, leather, biological stains and indicators, spirit varnishes and wood stains, and pigments. In addition, it has been used as a component of oxidation-type hair formulations. Two hundred and thirty-three million pounds of 2,4-diaminotoluene were produced in the United States in 1976. In addition, 356,000 pounds were imported in that year.

A bioassay of 2,4-diaminotoluene for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and $B6C3F_1$ mice.

Groups of 50 rats of each sex were administered 2,4-diaminotoluene at one of two doses, initially either 125 or 250 ppm, for 40 weeks. Because of excessive depression in the amount of mean body weight gained in both low- and high-dose groups, doses were then reduced to 50 and 100 ppm, respectively. Administration of 50 ppm to the low-dose groups was continued for 63 weeks, and surviving animals in these groups were then killed. Surviving animals in the high-dose males and females administered 100 ppm were killed at the end of 39 and 44 weeks, respectively, due to morbidity. The time-weighted average dose was 79 ppm for the low-dose male and females for 103 weeks, 176 ppm for the high-dose males for 79 weeks, and 171 ppm for the high-dose females for 84 weeks. Matched controls consisted of 20 untreated rats of each sex.

Groups of 50 mice of each sex were administered 2,4-diaminotoluene at one of two doses, either 100 or 200 ppm, for 101 weeks. Matched controls consisted of 20 untreated mice of each sex. Surviving mice were killed at the end of administration of the test chemical.

Mean body weights of dosed male and female rats and mice were lower than those of corresponding controls and were dose related except for the low-dose male mice, for which mean body weights were only slightly lower than those of controls. Mortality was not dose related in either the male or female mice, but was dose related in both the male and female rats. Survival was decreased and lesions of hepatonephrotoxicity were observed in the animals administered the 2,4-diaminotoluene.

In the rats, hepatocellular carcinomas or neoplastic nodules occurred at incidences that were dose related in both the males ($P = 0.014$) and the females ($P = 0.008$). In direct comparisons of incidences of the tumors in control and dosed groups, the incidence in the high-dose male group had a P value of 0.026 (males: controls 0/20, low-dose 5/49, high-dose 10/50; females: controls 0/20; low-dose 0/50, high-dose 6/49). The significance of the occurrence of these tumors in both the male and female rats was supported by the high incidences of associated nonneoplastic lesions of the liver in the dosed groups and by low incidences of liver tumors in historical-control male or female F344 rats at the same laboratory.

In addition, carcinomas or adenomas of the mammary gland occurred in the female rats at incidences that were dose related ($P = 0.002$) and in direct comparisons were

higher in the dosed groups ($P<0.001$) than in the control group (control 1/20; low-dose 38/50, high-dose 41/50).

In male rats, fibromas of the subcutaneous tissue occurred at incidences that were dose related ($P=0.004$) and in direct comparisons were higher in the dosed groups ($P\leq 0.020$) than in the control group (controls 0/20, low-dose 15/30, high-dose 19/50).

In the mice, hepatocellular carcinomas occurred in the females at incidences that were dose related ($P=0.002$) and in direct comparisons were higher in dosed groups ($P\leq 0.007$) than in the control group (controls 0/19, low-dose 13/47, high-dose 18/46). In addition, lymphomas occurred at a significant incidence ($P<0.001$) in the low-dose female mice (controls 2/19, low-dose 29/47, high-dose 11/46). No tumors occurred at significantly increased incidences in the dosed male mice.

Under the conditions of this bioassay, 2,4-diaminotoluene was carcinogenic for F344 rats, inducing hepatocellular carcinomas or neoplastic nodules in both males and females and carcinomas or adenomas of the mammary gland in females. The test chemical was also carcinogenic for female $B6C3F_1$ mice, inducing hepatocellular carcinomas. The incidence of lymphomas in the female mice suggested that these tumors may also have been related to administration of the test chemical.

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Positive
Female Rats:	Positive
Male Mice:	Negative
Female Mice:	Positive

TR-163 Bioassay of Calcium Cyanamide for Possible Carcinogenicity (CAS No. 156-62-7)

Calcium cyanamide was first synthesized in 1898 and became one of the earliest successes in nitrogen fixation. The commercially formulated product contains approximately 65% calcium cyanamide, which is 20 to 24% nitrogen. For most of the 20th century it has been used as a fertilizer, and also as a cotton defoliant, herbicide, and soil insecticide. Its use as a fertilizer has diminished in recent years due to the introduction of other compounds, so that the chief industrial uses of calcium cyanamide today stem from the reactivity of the nitrile group. Calcium cyanamide can be dimerized to dicyandiamide, an intermediate for melamine, one of the basic ingredients in amino plastics and resins. Other products prepared from calcium cyanamide include urea, thiourea, and guanidine. Fusion of calcium cyanamide with sodium chloride produces calcium cyanide, which is required for ore processing and the production of ferrocyanides. Calcium cyanamide is added to pig iron to impart nitrogen and to remove sulfur from steel.

A bioassay of formulated calcium cyanamide for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and $B6C3F_1$ mice.

Groups of 50 rats of each sex were administered a commercial formulation containing 63% calcium cyanamide in the diet at one of two doses, either 100 or 200 ppm for the males and either 100 or 400 ppm for the females, for 107 weeks. Groups of 50 mice of each sex were administered the test chemical at one of two doses, either 500 or 2,000 ppm, for 100 weeks. Matched controls consisted of 20 untreated rats and 20 untreated mice of each sex. All surviving animals were killed at the end of administration of the test chemical.

Mean body weights of the dosed rats and mice were only slightly lower than those of corresponding controls, except for the low-dose female mice, whose mean body weights were unaffected by the test chemical. Mortality was dose related only in male mice. Survival was 70% or greater in all dosed and control groups of each species and sex at the end of the bioassay, and sufficient numbers of animals were at risk in all groups for the development of late-appearing tumors. Both rats and mice may have been able to tolerate higher doses.

No tumors occurred in the dosed rats of either sex at incidences that could clearly be related to administration of the calcium cyanamide. However, in the subchronic studies performed with the rats, calcium cyanamide was found to cause diffuse follicular hyperplasia of the thyroid, with periglandular fibrosis and prominent periglandular vascularity.

In male mice, hemangiosarcomas were dose related in the males ($P=0.006$); however, in direct comparisons, incidences in the individual dosed groups were not significantly higher than those in the control group (controls 1/20 (5%); low-dose 2/50 (4%); high-dose 10/50 (20%)). The incidence of these tumors in historical-control male $B6C3F_1$ mice was (13/323 (4%)), and the highest incidence observed was 2/19 (10%). In female mice, lymphomas or leukemias were dose related ($P=0.009$), and in a direct comparison the incidence of these tumors in the high-dose group was significantly higher ($P=0.006$) than that in the control group (controls 1/20 (5%); low-dose 11/46 (24%); high-dose 18/50 (36%)); however, the incidence of the lymphomas or leukemias in historical-control female $B6C3F_1$ mice was 67/324 (21%), suggesting that the incidence of these tumors in the matched-control group of the present bioassay may have been abnormally low. Thus, neither the incidences of hemangiosarcomas of the circulatory system in male mice nor of lymphomas or leukemias in the female mice can clearly be related to administration of the test chemical.

It is concluded that under the conditions of this bioassay, the test formulation of calcium cyanamide was not carcinogenic for F344 rats or $B6C3F_1$ mice of either sex.

Synonyms: cyanamide; CaNCN

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative
Male Mice:	Negative
Female Mice:	Negative

TR-164 Bioassay of N-Nitrosodiphenylamine for Possible Carcinogenicity (CAS No. 86-30-6)

N-Nitrosodiphenylamine is a nitrosoamine which is used as a vulcanization retarder in curing natural rubber and the synthetic elastomers styrenebutadiene and nitrile-butadiene. U.S. production in 1976 was 1.3 million pounds.

A bioassay of N-nitrosodiphenylamine for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and $B6C3F_1$ mice.

Groups of 50 rats of each sex were administered N-nitrosodiphenylamine at one of two doses, either 1,000 or 4,000 ppm, for 100 weeks. Matched controls consisted of 20 untreated rats of each sex. All surviving rats were killed at the end of administration of the test chemical.

Groups of 50 male mice were administered N-nitrosodiphenylamine at one of two doses, either 10,000 or 20,000 ppm, for 101 weeks. Groups of 50 female mice were administered the test chemical at one of two doses, initially 5,000 or 10,000 ppm, for 38 weeks. Because of excessive depression in the amount of mean body weight gained in the dosed groups, the doses for the females were then reduced to 1,000 and 4,000 ppm, respectively, and administration at the lowered doses was continued for 60 weeks. The time-weighted average doses for the female mice were either 2,315 or 5,741 ppm. Matched controls consisted of 20 untreated mice of each sex. All surviving mice were killed at the end of administration of the test chemical.

Mean body weights of dosed rats and mice of each sex were lower than those of corresponding controls, and were dose related throughout the bioassay, except for those of female rats during the first part of the bioassay. Mortality was dose related in the female rats, but was not affected when the test chemical was administered to the male rats or the male or female mice. Survival at the end of the bioassay was 64% or greater in the dosed and control groups of rats and mice of each sex, and sufficient numbers of animals were at risk in all groups for the development of late-appearing tumors.

Transitional-cell carcinomas of the urinary bladder occurred at incidences that were dose related ($P \leq 0.001$) in both male and female rats, and in direct comparisons the incidences of these tumors in the high-dose groups of each sex were significantly higher ($P \leq 0.001$) than those in the corresponding controls (males: controls 0/19; low-dose 0/46; high-dose 16/45; females: controls 0/18; low-dose 0/48; high-dose 40/49). The possible mechanism by which these tumors were induced, such as calculi formation in the bladder or nitrosation of amines present in feed to a carcinogenic nitrosoamine, is unknown.

Fibromas of the integumentary system occurred in male rats at incidences that were dose related ($P = 0.003$), although in direct comparisons the incidences of these tumors in the individual dosed groups were not significantly higher than those in the control group (controls 1/20, or 5%; low-dose 1/50, or 2%; high-dose 10/50, or 20%). The incidence of fibromas of the integumentary system in historical-control male F344 rats at this laboratory is 6/285, or 2%. These results suggest an association of the fibromas in the male rats with the administration of the test chemical.

No tumors occurred in the mice of either sex at incidences that were significantly higher in the dosed groups than in the corresponding control groups. The only changes related to compound administration were chronic inflammatory lesions in the urinary bladders of dosed mice.

It is concluded that under the conditions of this bioassay, N-nitrosodiphenylamine was carcinogenic for both sexes of F344 rats, including transitional-cell carcinomas of the urinary bladder, but was not carcinogenic for $B6C3F_1$ mice of either sex.

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Positive
Female Rats:	Positive
Male Mice:	Negative
Female Mice:	Negative

TR-165 Bioassay of 4-Chloro-o-toluidine Hydrochloride for Possible Carcinogenicity (CAS No. 3156-93-3)

4-Chloro-o-toluidine hydrochloride is used commercially as an intermediate for dyestuffs intended for textiles, e.g., pigment yellow 49 and pigment red 7, as well as C.I, 12800, azoic coupling component 8, and azoic diazo component 11.

A bioassay of 4-chloro-o-toluidine hydrochloride for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and $B6C3F_1$ mice.

Groups of 50 rats of each sex were administered 4-chloro-o-toluidine in the diet at one of two doses, either 1,250 or 5,000 ppm, for 107 weeks. Groups of 50 mice of each sex were administered the test chemical in the diet at one of two doses, either 3,750 or 15,000 ppm for the males and either 1,250 or 5,000 ppm for females, for 99 weeks, except for the high dose females (92 weeks). Matched controls consisted of 20 untreated rats and 20 untreated mice of each sex. All surviving animals were killed at the end of administration of the test chemical.

Mean body weights of the high-dose rats and the low- and high-dose mice of each sex were lower than those of corresponding controls, and those of the mice were dose related. Mortality was not significantly affected by administration of the test chemical to rats of either sex

and survival was 75% or greater at the end of the study in dosed and control groups. Sufficient numbers of rats were at risk for the development of late-appearing tumors. In mice, mortality was dose related for each sex.

In rats no tumors occurred at incidences which could clearly be related to administration of the test chemical.

In both male and female mice, hemangiosarcomas occurred at incidences that were dose related ($P \leq 0.001$), and in direct comparisons the incidences in the high-dose males and the low- and high-dose females were significantly higher ($P < 0.001$) than those in the corresponding controls (males: controls 0/20; low-dose 3/50; high-dose 37/50; females: controls 0/18; low-dose 40/49, high-dose 39/50). The combined incidences of hemangiosarcomas and hemangiomas also were dose related and were significantly higher in the dosed groups of male and female mice than in the corresponding controls. There was a high incidence of hemosiderin deposit in the renal tubular epithelium, particularly in mice with hemangiosarcomas.

It is concluded that under the conditions of this bioassay, 4-chloro-o-toluidine hydrochloride was not carcinogenic for F344 rats but was carcinogenic for $B6C3F_1$ mice, including hemangiosarcomas and hemangiomas in both males and females.

Synonym: 2-amino-4-chlorotoluene hydrochloride

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative
Male Mice:	Positive
Female Mice:	Positive

TR-166 Bioassay of Tetraethylthiuram Disulfide for Possible Carcinogenicity (CAS No. 97-77-9)

Tetraethylthiuram disulfide is known in the rubber industry as ethyl tuads where it is used in compounding natural rubber and the synthetic elastomers isobutylene-isoprene, butadiene, styrene-butadiene, isoprene, and nitrile-butadiene rubber. It is used both as a rubber accelerator and vulcanizing agent, as an activator of thiazole accelerators, and as a plasticizer in neoprene. Current estimates indicate that 510,000 to 550,000 kilograms of chemical are produced annually worldwide.

A bioassay of technical-grade tetraethylthiuram disulfide for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and $B6C3F_1$ mice.

Groups of 50 rats of each sex were administered tetraethylthiuram disulfide in the diet at one of two doses, either 300 or 600 ppm, for 107 weeks. Groups of 50 mice of each sex were administered the test chemical at one of two doses, either 500 or 2,000 ppm for the males and either 100 or 500 ppm for the females, for 108 weeks. Matched controls consisted of 20 untreated rats and 20 untreated mice of each sex. All surviving animals were killed at the ends of the periods of administration of the test chemical.

Mean body weights of the dosed rats and mice of each sex were lower than those of corresponding controls and were dose related throughout most of the bioassay. Mortality was not significantly affected by administration of the test chemical to either the rats of the mice, except for the female rats, in which the mortality was higher in the control group than in the dosed groups; however, the survival at the end of the bioassay was 65% or greater in all dosed and control groups of rats and mice of either sex, and sufficient numbers of animals were at risk in each group for the development of late-appearing tumors.

No tumors occurred in the rats or mice of either sex at incidences that were significantly higher in dosed groups than in corresponding control groups.

It is concluded that under the conditions of this bioassay, tetraethylthiuram disulfide was not carcinogenic for F344 rats or $B6C3F_1$ mice of either sex.

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative
Male Mice:	Negative
Female Mice:	Negative

TR-167 N-Butylurea (CAS: 592-31-4) Sodium Nitrite (CAS: 7632-00-0)

Data considered to be inconclusive and not reportable; no Technical Report issued.

TR-168 Bioassay of N-(1-Naphthyl) ethylenediamine Dihydrochloride for Possible Carcinogenicity (CAS No. 1465-25-4)

N-(1-Naphthyl)ethylenediamine dihydrochloride, a diagnostic reagent derived from 1-naphthylamine, was selected for bioassay by the National Cancer Institute because of the suspected carcinogenicity of its parent compound, and the confirmed bladder carcinogenicity of the related compound 2-naphthylamine in humans.

A bioassay for the possible carcinogenicity of N-(1-naphthyl)ethylenediamine dihydrochloride was conducted using Fischer 344 rats and $B6C3F_1$ mice. N-(1-Naphthyl)ethylenediamine dihydrochloride was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. Twenty-five rats of each sex and 50 mice of each sex were placed on test as controls. The high and low dietary concentrations of N-(1-naphthyl)ethylenediamine dihydrochloride administered to rats and male mice were 0.1 and 0.05 percent, respectively. The high and low time-

weighted average concentrations administered to female mice were, respectively, 0.3 and 0.2 percent. The compound was administered in the diet for 104 weeks, followed by an observation period of 4 weeks for high dose rats, 3 weeks for low dose rats, low dose female mice, and high dose female mice, and 1 week for high dose male mice.

There were no significant positive associations between the concentrations of N-(1-naphthyl) ethylenediamine dihydrochloride administered and mortality in rats of either sex or in male mice. There was a significant positive association between concentration and mortality in female mice. In all groups, except for high dose females, adequate numbers of animals survived sufficiently long to be at risk from late-developing tumors. Mean body weight depression, in relation to controls, was apparent for both sexes of rats and mice, indicating that higher concentrations of the test chemical would not have been tolerated by these animals.

In rats or mice of either sex, there were no statistically significant positive associations between the concentration of N-(1-naphthyl)ethylenediamine dihydrochloride and tumor incidence.

Under the conditions of this bioassay, dietary administration of N-(1-naphthyl)ethylenediamine dihydrochloride was not carcinogenic in Fischer 344 rats or $B6C3F_1$ mice.

Synonyms: N-1-Naphthalenyl-1,2-ethanediamine dihydrochloride; N-1-Naphthylethylenediamine dihydrochloride

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative
Male Mice:	Negative
Female Mice:	Negative

TR-169 Bioassay of 2-Nitro-p-phenylenediamine for Possible Carcinogenicity (CAS No. 5307-14-2)

2-Nitro-p-phenylenediamine. a component of both semipermanent and permanent hair dye formulations, was selected for bioassay by the National Cancer Institute because of the increased incidence of bladder cancer among dye manufacturing industry workers. Aromatic amines are one of several classes of organic chemicals thought to contribute to the increased cancer risk in this industry. The widespread exposure to 2-nitro-p-phenylenediamine among the general population, and the possibility of an increased cancer risk among hairdressers were additional factors in the selection of this compound for testing.

A bioassay for the possible carcinogenicity of 2-nitro-p-phenylenediamine was conducted using Fischer 344 rats and $B6C3F_1$ mice. 2-Nitro-p-phenylenediamine was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. Twenty animals of each sex and species were placed on test as controls. The high and low dietary concentrations of 2-nitro-p-phenylenediamine were, respectively, 1,100 and 550 ppm for male rats, 2,200 and 1,100 ppm for female rats, and 4,400 and 2,200 ppm for mice of both sexes. The compound was administered in the diet for 78 weeks, followed by an observation period of 27 weeks for rats and 12 to 13 weeks for mice.

There were no significant positive associations between the dietary concentrations of 2-nitro-p-phenylenediamine administered and mortality in rats and mice of either sex. Adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. Mean body weight depression, relative to controls, was observed in dosed rats and mice of both sexes, indicating that the concentrations administered to these animals may have approximated the maximum tolerated dosages.

When the female mice in each group, having hepatocellular carcinoma or hepatocellular adenoma, were combined and the resulting incidences statistically analyzed, there was a significant positive association between concentration administered and the incidence of these tumors. This finding was supported by a significant high dose to control Fischer exact comparison. No tumors occurred in statistically significant increased incidences when dosed male or female rats or male mice were compared to their respective controls.

Under the conditions of this bioassay, dietary administration of 2-nitro-p-phenylenediamine was carcinogenic to female $B6C3F_1$ mice, causing an increased incidence of hepatocellular neoplasms, primarily hepatocellular adenomas. There was no convincing evidence for the carcinogenicity of the compound in Fischer 344 rats or in male $B6C3F_1$ mice.

Synonyms: 2-Nitro-1,4-benzenediamine; Diaminonitrobenzene; m-Nitro-p-phenylenediamine; o-Nitro-p-phenylenediamine; 2-Nitro-1,4-diaminobenzene; 1,4-Diamino-2-nitrobenzene; 2-NP; 2-NPPD; 2-N-p-PDA; Ursol Brown RR; Zoba Brown RR; Fourrine Brown 2R; Fourrine 36; Fouramine 2R; C.I. Oxidation Base 22

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative
Male Mice:	Negative
Female Mice:	Positive

TR-170 Bioassay of a Solution of β-Nitrostyrene and Styrene for Possible Carcinogenicity (CAS No. 102-96-5, CAS No. 100-42-5)

β-Nitrostyrene was selected for bioassay by the National Cancer Institute because of a lack of adequate

carcinogenicity data. The compound is usually supplied as a 30 percent solution in styrene and this commercial product was selected as the material to be tested.

β-Nitrostyrene is used as a chain stopper in styrene type polymerization reactions for the production of polystyrene plastics, synthetic rubber, and resins. β-Nitrostyrene also possesses antibacterial, antifungal, and insecticidal activities and has been suggested for use as a repellent for bats and other rodents; however, this compound does not appear to be currently registered for pesticide use with the U.S. Environmental Protection Agency.

A bioassay of a solution of 30 percent β-nitrostyrene and 70 percent styrene for possible carcinogenicity was conducted using Fischer 344 rats and B6C3F$_1$ mice. The solution of the two test materials in corn oil was administered by gavage, at either of two dosages, to groups of 50 male and 50 female animals of each species. The high and low dosages utilized in the study were, respectively, 300 and 150 mg/kg for male rats; 150 and 75 mg/kg for female rats; and 175 and 87.5 mg/kg for mice of both sexes. These dosages are expressed in terms of the β-nitrostyrene contained in the styrene solution. Twenty animals of each species and sex were placed on test as controls, and were gavaged with corn oil on the same schedule as dosed animals.

A 79-week period of chemical administration was followed by an additional observation period of 29 weeks for rats, and a 78-week period of chemical administration was followed by an additional 14-week observation period for mice.

There was no significant difference between the survival of rats dosed with the test solution and that of their controls, and there was no significant association between dosage and mortality among female mice. There was a significant positive association between dosage and mortality among male mice; however, adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. There was distinct mean body weight depression when high dose female mice or male rats were compared to their controls, indicating that the dosage administered to these animals may have approximated the maximum tolerated dosage. Since no distinct mean body weight depression, no significantly accelerated mortality, and no other toxic effects were associated with the administration of β-nitrostyrene and styrene to female rats or male mice, it is possible that these animals may have been able to tolerate a higher dosage.

There were no significant positive associations between administration of the solution and increased tumor incidence in rats of either sex.

When those male mice having either alveolar/bronchiolar carcinomas or alveolar/bronchiolar adenoma were combined and the resulting tumor incidences for each group were statistically analyzed, the low dose to control Fischer exact comparison was significant. The Cochran-Armitage test and the high dose to control comparison, however, were not. No other tests for tumors of any site in either male or female mice were significant.

Under the conditions of this bioassay, there was no convincing evidence for the carcinogenicity of a solution of β-nitrostyrene and styrene in Fischer 344 rats or in B6C3F$_1$ mice.

Synonyms for β-Nitrostyrene: (2-Nitroethenyl)benzene; ω-Nitrostyrene; BNS

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative
Male Mice:	Negative
Female Mice:	Negative

TR-171 Bioassay of 2,4-Dimethoxyaniline Hydrochloride for Possible Carcinogenicity (CAS No. 54150-69-5)

2,4-Dimethoxyaniline hydrochloride, the hydrochloride salt of the dye intermediate 2,4-dimethoxyaniline, was selected for bioassay by the National Cancer Institute because of the increased incidence of bladder cancer among dye manufacturing industry workers. Aromatic amines are one of several classes of chemicals thought to contribute to the increased cancer risk in this industry.

A bioassay for the possible carcinogenicity of 2,4-dimethoxyaniline HCl was conducted using Fischer 344 rats and B6C3F$_1$ mice. 2,4-Dimethoxyaniline HCl was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. Twenty animals of each sex and species were placed on test as controls. The high and low dietary concentrations of 2,4-dimethoxyaniline HCl were, respectively, 3,000 and 1,500 ppm for rats and 5,000 and 2,500 ppm for mice. The compound was administered in the diet for 104 weeks to rats and 103 weeks to mice, followed by a 1-week observation period for both species.

There were no significant positive associations between the concentrations of 2,4-dimethoxyaniline HCl administered and mortality in rats or mice of either sex. Adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. Dose-related mean body weight depression was observed for females of both species, indicating that the concentrations of 2,4-dimethoxyaniline HCl administered to these groups may have approximated the maximum tolerated concentrations. Compound-related mean body weight depression was only slight for male rats and was apparent in male mice only until week 50; however follicular-cell hyperplasias and cystic follicles of the thyroid were observed in dosed male mice, suggesting that the concentrations the male mice received may have approximated the maximum tolerated concentrations. Since no distinct mean body weight depression in relation to controls, no significant accelerated mortality, and no other signs of toxicity were associated with

administration of 2,4-dimethoxyaniline HCl to male rats, it is possible that these animals may have been able to tolerate a higher dietary concentration.

There was a significant positive trend between concentration of the test chemical and the incidence of a combination of hepatocellular carcinomas and adenomas in male mice and an increase in the combination of these lesions in female mice. However, no statistically significant differences in tumor incidence at any site were observed when dosed rats and mice were compared to their respective controls.

Under the conditions of this bioassay there was no convincing evidence for the carcinogenicity of 2,4-dimethoxyaniline HCl in Fischer 344 rats or $B6C3F_1$ mice.

Synonyms: 2,4-dimethoxybenzenamine hydrochloride; 4-methoxy-o-anisidine hydrochloride; 2-methoxy-p-anisidine hydrochloride

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative
Male Mice:	Negative
Female Mice:	Negative

TR-172 Bioassay of Sodium Diethyldithiocarbamate for Possible Carcinogenicity (CAS No. 148-18-5)

Sodium diethyldithiocarbamate is a chelating agent used primarily in the analytical determination of copper, arsenic, nickel, and other metals. Other applications include the detection of toxic metals in urine, and in the treatment of human poisoning with metals.

A bioassay of sodium diethyldithiocarbamate for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and $B6C3F_1$ mice.

Groups of 50 rats of each sex were administered sodium diethyldithiocarbamate at one of two doses, either 1,250 or 2,500 ppm, for 104 weeks. Groups of 50 mice of each sex were administered sodium diethyldithiocarbamate at one of two doses, either 500 or 4,000 ppm, for 108 or 109 weeks. Matched controls consisted of 16 untreated male rats, 20 untreated female rats and 20 untreated mice of each sex. All surviving rats and mice were killed at the end of administration of the test chemical.

Mean body weights of all dosed groups of rats and mice were lower that those of corresponding controls and were dose related throughout the bioassay except those of the low-dose male rats, which were essentially unaffected by administration of the test chemical. Survivals of the rat and mice were unaffected, and no other clinical signs could be related to administration of the test chemical; thus, the animals may have been able to tolerate higher doses. Sufficient numbers of dosed and control animals of each species and sex were at risk for the development of late-appearing tumors.

No tumors occurred in the rats or mice of either sex at incidences that were significantly higher in the dosed groups than in the control groups.

It is concluded that under the conditions of this bioassay, sodium diethyldithiocarbamate was not carcinogenic for F344 rats or $B6C3F_1$ mice of either sex.

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative
Male Mice:	Negative
Female Mice:	Negative

TR-173 Bioassay of Carbromal for Possible Carcinogenicity (CAS No. 77-65-6)

Carbromal, a mild central nervous system depressant, was selected for bioassay by the National Cancer Institute because of the similarity of the biological activity of this compound to that of urethan, which is known to induce leukemia in mice and is an initiator of skin carcinogenesis in mice, and the widespread exposure to this compound among the general population via deliberate ingestion for medicinal purposes.

A bioassay for the possible carcinogenicity of carbromal was conducted using Fischer 344 rats and $B6C3F_1$ mice. Carbromal was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species with the exception of 49 low dose male mice and high dose female mice. Twenty animals of each sex and species were placed on test as controls. The high and low dietary concentrations of carbromal were, respectively, 2,500 and 1,250 ppm for rats and 2,500 and 1,250 ppm for mice. The compound was administered for 103 weeks to rats and for 78 weeks to mice. The period of compound administration was followed by an observation period of 1 week for rats and 26 weeks for mice.

There was no significant positive associations between the concentrations of carbromal administered and mortality in rats or mice of either sex. Adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. Slight dose-related mean body weight depression was observed for male rats and for females of both species and the mean body weight among dosed male mice was lower than that for controls, indicating that the concentrations of carbromal administered to the animals in this bioassay may have approximated the maximum tolerated concentrations.

None of the statistical tests for any site in female rats or in mice of either sex indicated a significant positive association between compound administration and tumor incidence. There was a significant positive association between the concentrations administered and the incidences of adrenal pheochromocytomas in male rats; however, the Fischer exact comparisons were not significant.

Under the conditions of this bioassay, dietary administration of carbromal was not carcinogenic in Fischer 344 rats or B6C3F$_1$ mice.

Synonyms: N-(aminocarbonyl)-2-bromo-2-ethyl-butanamide; (2-bromo-2-ethylbutyryl)urea, bromodiethylacetylcarbamide; bromodiethylacetylurea; (α-bromo-α-ethylbutyryl)carbamide

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative
Male Mice:	Negative
Female Mice:	Negative

TR-174 Bioassay of p-Phenylenediamine Dihydrochloride for Possible Carcinogenicity (CAS No. 624-18-0)

p-Phenylenediamine dihydrochloride, a hydrochloride salt of p-phenylenediamine, the major component of many oxidation hair dyes, was selected for bioassay by the National Cancer Institute because of the increased incidence of bladder cancer reported among dye manufacturing industry workers. Aromatic amines are one of several classes of chemicals thought to contribute to this increased cancer risk. The widespread exposure to p-phenylenediamine among the general population and the increased cancer risk among hairdressers were additional factors in the selection of p-phenylenediamine dihydrochloride for testing.

A bioassay of p-phenylenediamine dihydrochloride for possible carcinogenicity was conducted using Fischer 344 rats and B6C3F$_1$ mice. p-Phenylenediamine dihydrochloride was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. The high and low concentrations of p-phenylenediamine dihydrochloride were, respectively, 1,250 and 625 ppm for both rats and mice. After a 103-week period of compound administration, there were additional observation periods of 2 weeks for rats and 1 week for mice. Twenty animals of each sex and species were placed on test as controls.

There were no significant positive associations between the concentrations of p-phenylenediamine dihydrochloride administered and mortality in rats or mice of either sex. Adequate numbers of animals in all groups survived sufficiently long to be at risk from late developing tumors. Slight dose-related mean body weight depression was observed in female rats and the mean body weights among high dose male rats and dosed female mice were slightly depressed in relation to their respective controls, indicating that the concentrations of p-phenylenediamine dihydrochloride administered to these animals in this bioassay may have approximated the maximum tolerated concentrations. Since no distinct mean body weight depression relative to controls, no significant accelerated mortality, and no other signs of toxicity were associated with administration of p-phenylenediamine dihydrochloride to male mice, it is possible that these animals may have been able to tolerate a higher dietary concentration.

None of the statistical tests for any site in rats or mice of either sex, including time to leukemia or malignant lymphoma analysis in female mice, indicated a significant positive association between compound administration and tumor incidence.

Under the conditions of this bioassay, there was no convincing evidence that dietary administration of p-phenylenediamine dihydrochloride was carcinogenic in Fischer 344 rats or B6C3F$_1$ mice.

Synonyms: 1,4-benzenediamine dihydrochloride; p-PDA HCl; p-OD HCl; p-phenylenediamine di-HCl; Durafur Black RC; Fourrine DS; Fourrine 64; Pelagol Grey CD; C.I. Oxidation Base 10A

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative
Male Mice:	Negative
Female Mice:	Negative

TR-175 Bioassay of Lithocholic Acid for Possible Carcinogenicity (CAS No. 434-13-9)

Lithocholic acid, a naturally occurring bile acid, was selected for bioassay by the National Cancer Institute because it has been reported to promote the development of hepatoma and hyperplastic nodules induced by DL-ethionine in rat liver, and because of the strong correlation between concentrations of neutral sterols and bile acid derivatives in human feces and the incidence of human colon cancer.

A bioassay for the possible carcinogenicity of lithocholic acid was conducted using Fischer 344 rats and B6C3F$_1$ mice. Lithocholic acid was administered by gavage, at either of two dosages, to groups of 50 male and 50 female animals of each species, except for 49 low dose female rats. Twenty animals of each sex and species were placed on test as controls. The high and low dosages of lithocholic acid administered were, respectively, 500 and 250 mg/kg for rats and 250 and 125 mg/kg for mice. The compound was administered to rats and mice for 103 weeks. The period of compound administration was followed by an observation period of 1 week for rats and 2 weeks for mice.

There were no significant positive associations between the dosages of lithocholic acid administered and mortality in rats or mice of either sex. Adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. Slight dose-related mean body weight depression was observed in male rats

and female mice and high incidences of chronic kidney inflammation were observed in female rats, indicating that the dosages of lithocholic acid administered to these animals in this bioassay may have approximated the maximum tolerated dosages. Since no mean body weight depression, relative to controls, no significant accelerated mortality, and no other signs of toxicity were associated with administration of lithocholic acid to male mice, it is possible that these animals may have been able to tolerate a higher dosage. However, in the subchronic study there were deaths among all dosed male mouse groups, even those receiving lithocholic acid at a level only twofold greater than the high dose utilized in the chronic study.

None of the statistical tests for any site in rats or in mice of either sex indicated a significant positive association between compound administration and tumor incidence.

Under the conditions of this bioassay, lithocholic acid was not carcinogenic when administered by gavage to Fischer 344 rats or B6C3F$_1$ mice.

Synonyms: (3α,5β)-3-Hydroxycholan-24-oic acid; 3α-Hydroxy-5β-cholan-24-oic acid; 3α-Hydroxy-5β-cholanic acid; 3α-Hydroxychloanic acid; 3-Monohydroxycholanic acid; 17β-(1-methyl-3-carboxypropyl)ethiocholan-3α-ol.

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative
Male Mice:	Negative
Female Mice:	Negative

TR-176 N,N-Dimethyl-P-Nitrosoaniline (CAS: 138-89-6)

Data considered to be inconclusive and not reportable; no Technical Report issued.

TR-177 Bioassay of 4'-(Chloroacetyl)-acetanilide for Possible Carcinogenicity (CAS No. 140-49-8)

4'-(Chloroacetyl)-acetanilide, an intermediate in the synthesis of dyes and pharmaceutical compounds, was selected for bioassay by the National Cancer Institute because of the increased incidence of bladder cancer observed among dye manufacturing industry workers. Aromatic amines, such as 4'-(chloroacetyl)-acetanilide, are among several classes of chemicals thought to contribute to the increased cancer risk in this industry, and 4'-(chloroacetyl)-acetanilide is especially suspect because it is structurally similar to the possible human renal pelvic carcinogen, phenacetin.

A bioassay for the possible carcinogenicity of 4'-(chloroacetyl)-acetanilide was conducted using Fischer 344 rats and B6C3F$_1$ mice. 4'-(Chloroacetyl)-acetanilide was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. Twenty animals of each sex and species were placed on test as controls. The high and low dietary concentrations of 4'-(chloroacetyl)-acetanilide were, respectively, 2,000 and 1,000 ppm for rats and 10,000 and 5,000 ppm for mice. The compound was administered for 87 weeks of a 102-week period in rats and for 90 weeks of a 105-week period in mice. Mice were killed at the end of the last week of compound administration, while rats were observed for 1 week after compound administration ceased.

There were no significant positive associations between the concentration of 4'-(chloroacetyl)-acetanilide administered and mortality in rats or mice of either sex. Adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. Dose-related mean body weight depression was observed for males and females of both species, indicating that the concentrations of 4'-(chloroacetyl)-acetanilide administered to the animals in this bioassay may have approximated the maximum tolerated concentrations.

None of the statistical tests for any site in rats of either sex or in male mice indicated a significant positive association between compound administration and tumor incidence. Although there was a significant positive association between the concentration of the compound administered and the incidences of hepatocellular adenomas in female mice, the Fischer exact comparisons were not significant.

Under the conditions of this bioassay, 4'-(chloroacetyl)-acetanilide was not carcinogenic when administered in the diet to Fischer 344 rats or B6C3F$_1$ mice of either sex.

Synonyms: N'-(Chloroacetyl)-N-phenylacetamide; 4-(Cl-acetyl)acetanilide

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative
Male Mice:	Negative
Female Mice:	Negative

TR-178 Bioassay of 2-(Chloromethyl) pyridine Hydrochloride for Possible Carcinogenicity (CAS No. 6959-47-3)

2-(Chloromethyl)pyridine hydrochloride, an aromatic heterocycle used in a variety of syntheses, was selected for bioassay by the National Cancer Institute because of the structural similarity of this compound to 2-(α,β-dichloroethyl)-pyridine hydrochloride, a carcinogen in rats, mice, Syrian hamsters, and Mongolian gerbils.

A bioassay for the possible carcinogenicity of 2-(chloromethyl)pyridine hydrochloride was conducted using Fischer 344 rats and B6C3F$_1$ mice. 2-(Chloromethyl)pyridine hydrochloride was administered by gavage, at either of two dosages, to groups of 50 male and 50 female animals of each species, with the exception of 49 male rats in the high dose group. Twenty animals of each sex and species were placed on test as vehicle controls. The high and low dosages of 2-(chloromethyl)pyridine hydrochloride administered were, respectively, 150 and 75 mg/kg for rats and 250 and 125 mg/kg for mice. The compound was administered for 99 weeks to rats and mice. The period of compound administration was followed by an observation period of 6 weeks for rats and 5 weeks for mice.

There were no significant positive associations between the dosages of 2-(chloromethyl)pyridine hydrochloride administered and mortality in rats or mice of either sex. Adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. Slight dose-related mean body weight depression was observed in mice of both sexes, indicating that the dosages of 2-(chloromethyl)pyridine hydrochloride administered to these animals in this bioassay may have approximated the maximum tolerated concentrations. Since no distinct mean body weight depression relative to vehicle controls, no significant accelerated mortality, and no other signs of toxicity were associated with administration of 2-(chloromethyl) pyridine hydrochloride to rats, it is possible that these animals may have been able to tolerate a higher dosage.

None of the statistical tests for any site in female rats or in mice of either sex indicated a significant positive association between compound administration and tumor incidence. There was a significant positive trend between the dosages administered and the incidences of subcutaneous fibromas in male rats. The Fischer exact comparisons, however, were not significant.

Under the conditions of this bioassay, administration of 2-(chloromethyl)pyridine hydrochloride was not carcinogenic to Fischer 344 rats or B6C3F$_1$ mice.

Synonyms: 2-(Cl-methyl)pyridine HCl; 2-pyridylmethyl chloride hydrochloride; 2-picolyl chloride hydrochloride

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative
Male Mice:	Negative
Female Mice:	Negative

TR-179 Bioassay of p-Quinone Dioxime for Possible Carcinogenicity (CAS No. 105-11-3)

p-Quinone dioxime, a rubber vulcanization accelerator, was selected for bioassay by the National Cancer Institute because of a lack of adequate carcinogenicity data.

A bioassay for the possible carcinogenicity of p-quinone dioxime was conducted using Fischer 344 rats and B6C3F$_1$ mice. p-Quinone dioxime was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. Twenty animals of each sex and species were placed on test as controls, with the exception of 18 in the control male mouse group. The high and low concentrations of p-quinone dioxime were 750 and 375 ppm for rats and 1,500 and 750 ppm for mice. The compound was administered to rats and mice for 104 weeks. The period of compound administration was followed by an observation period of 1 week for both species.

There were no significant positive associations between the concentrations of p-quinone dioxime administered and mortality in rats or mice of either sex. Adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. Distinct dose-related mean body weight depression was observed among rats and slight mean body weight depression, relative to controls, was observed among mice, indicating that the dosages of p-quinone dioxime administered to the animals in this bioassay may have approximated the maximum tolerated concentrations.

Tumors of the urinary bladder were observed only in dosed rats. For female rats, there was a significant positive association between concentration administered and the incidences of a combination of urinary bladder neoplasms. The high dose to control Fischer exact comparison was also significant for these tumors in female rats. No compound-related neoplasms were observed in male rats or mice of either sex.

Under the conditions of this bioassay, dietary administration of p-quinone dioxime was carcinogenic to female Fischer 344 rats, causing neoplasms of the urinary bladder. The compound was not carcinogenic to male Fischer 344 rats or B6C3F$_1$ mice of either sex.

Synonyms: 2,5-cyclohexadiene-1,4-dione; dioxime p-benzoquinone; p-quinonedioxime; dioxime 1,4-cyclohexadienedione

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Positive
Male Mice:	Negative
Female Mice:	Negative

TR-180 Bioassay of 4-Nitro-o-phenylenediamine for Possible Carcinogenicity (CAS No. 99-56-9)

4-Nitro-o-phenylenediamine, a component of both semipermanent and permanent hair dye formulations,

was selected for bioassay by the National Cancer Institute because of the high incidence of bladder cancer reported among workers in the dye manufacturing industry.

A bioassay for the possible carcinogenicity of 4-nitro-o-phenylenediamine was conducted using Fischer 344 rats and B6C3F$_1$ mice. 4-Nitro-o-phenylenediamine was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. Twenty animals of each sex and species were placed on test as controls. The high and low dietary concentrations of 4-nitro-o-phenylenediamine were, respectively, 750 and 375 ppm for rats and 7500 and 3750 ppm for mice. The compound was administered for 103 weeks to rats and for 102 weeks to mice. The period of compound administration was followed by an observation period of 2 weeks for rats and mice.

There were no significant positive associations between the concentrations of 4-nitro-o-phenylenediamine administered and mortality in rats or mice of either sex. Adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. Distinct dose-related mean body weight depression was observed in mice, indicating that the concentrations of 4-nitro-o-phenylenediamine administered to these animals in this bioassay may have approximated the maximum tolerated concentrations. Since no distinct mean body weight depression relative to controls, no significantly accelerated mortality, and no other manifestations of chronic toxicity were associated with administration of 4-nitro-o-phenylenediamine to male or female rats, it is possible that these animals may have been able to tolerate a higher dietary concentration.

None of the statistical tests for any site in rats or in mice of either sex indicated a significant positive association between compound administration and tumor incidence.

Under the conditions of this bioassay, dietary administration of 4-nitro-o-phenylenediamine was not carcinogenic in Fischer 344 rats or B6C3F$_1$ mice.

Synonyms: 4-nitro-1,2-benzenediamine; 4-nitrophenylenediamine; 4-nitro-1,2-diaminobenzene; 1,2-diamino-4-nitrobenzene; 2-amino-4-nitroaniline; 4-NO; 4-NOP; 4-NOPD; 4-N-o-PDA; C.I. 76020

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative
Male Mice:	Negative
Female Mice:	Negative

TR-181 Bioassay of Michler's Ketone for Possible Carcinogenicity (CAS No. 90-94-8)

Michler's ketone, a dye intermediate and derivative of dimethylaniline, was selected for bioassay by the National Cancer Institute because of the elevated incidence of bladder cancer noted among dye manufacturing industry workers.

A bioassay for the possible carcinogenicity of technical-grade Michler's ketone was conducted using Fischer 344 rats and B6C3F$_1$ mice. Michler's ketone was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. Twenty animals of each sex and species were placed on test as controls. The high and low dietary concentrations of Michler's ketone were respectively, 500 and 250 ppm for male rats, 1,000 and 500 ppm for female rats, and 2,500 and 1,250 ppm for mice of both sexes. The compound was administered to rats and mice for 78 weeks. The period of compound administration was followed by an observation period of 28 weeks for male and high dose female rats, 29 weeks for low dose female rats and 13 weeks for mice.

There were significant positive associations between the concentrations of Michler's ketone administered and mortality in rats and mice of both sexes. Adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. There was distinct dose-related mean body weight depression in female rats and in mice of both sexes, and the mean body weight among dosed male rats was slightly lower than that in controls, indicating that the concentrations of Michler's ketone administered to these animals in this bioassay may have approximated the maximum tolerated concentrations.

There were significant positive associations between the concentrations of Michler's ketone administered and the incidences of hepatocellular carcinomas in both sexes of rats and in female mice and hemangiosarcomas in male mice. In all of these cases the high dose to control Fischer exact comparison was also significant.

Under the conditions of this bioassay, dietary administration of Michler's ketone was carcinogenic to male and female Fischer 344 rats and female B6C3F$_1$ mice, causing hepatocellular carcinomas, and to male B6C3F$_1$ mice, causing hemangiosarcomas.

Synonyms: bis[4-(dimethylamino)phenyl]methanone; 4,4'-bis(dimethylamino)benzophenone; p,p'-bis (dimethylamino)benzophenone; bis[p-(N,N'-dimethylamino) phenyl]ketone; tetramethyldiaminobenzophenone

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Positive
Female Rats:	Positive
Male Mice:	Positive
Female Mice:	Positive

TR-182 Acetamide (CAS: 60-35-5)

Data considered to be inconclusive and not reportable; no Technical Report issued.

TR-183 Bioassay of Dibutyltin Diacetate for Possible Carcinogenicity (CAS No. 1067-33-0)

Dibutyltin diacetate, a widely used catalyst for polymerization reactions, was selected for bioassay by the National Cancer Institute in an effort to screen a number of organo-metallic compounds for carcinogenicity.

A bioassay for the possible carcinogenicity of dibutyltin diacetate was conducted using Fischer 344 rats and $B6C3F_1$ mice. Dibutyltin diacetate was administered in the feed, at either of two concentrations, to groups of 50 male and female animals of each species. Twenty animals of each sex and species were placed on test as controls. The high and low time-weighted average dietary concentrations of dibutyltin diacetate were, respectively, 133 and 66.5 ppm for rats and 152 and 76 ppm for mice. The compound was administered for 78 weeks to rats and mice, followed by a period of no compound administration of 26 weeks for rats and 14 weeks for mice.

There were significant positive associations between the concentrations of dibutyltin diacetate administered and mortality in male rats and female mice. There were no significant positive associations between the concentrations administered and mortality in female rats or male mice. Adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. Mean body weight depression, relative to controls, was observed in male mice and significantly accelerated mortality, relative to controls, was observed in male rats and female mice, indicating that the concentrations of dibutyltin diacetate administered to these animals may have approximated the maximum tolerated concentrations. Since no mean body weight depression, no significantly accelerated mortality, and no other signs of toxicity were associated with administration of dibutyltin acetate to female rats, it is possible that these animals may have been able to tolerate a higher dietary concentration.

There were no neoplasms occurring in statistically significant higher incidences in dosed rats or mice when compared to their respective controls. However, there was an accidental loss of tissues from high dose female rats which precluded an evaluation of carcinogenicity in this group of animals. There was a significant positive association between the concentrations administered and the incidences of hepatocellular adenomas in females mice; however, the Fischer exact comparisons were not significant using the Bonferroni criterion. Liver neoplasms (i.e., a combination of adenomas and carcinomas) were also observed in male mice; however, the occurrence was not statistically significant.

Under the conditions of this bioassay, there was no conclusive evidence for the carcinogenicity of dibutyltin diacetate in male Fischer 344 rats or $B6C3F_1$ mice of either sex. The loss of tissues taken from high dose female rats in this bioassay precluded an evaluation of the carcinogenicity of dibutyltin diacetate to female Fischer 344 rats.

Synonyms: bis(acetyloxy)dibutylstannae; diacetoxydibutylstannae; diacetoxybutyltin; dibutyl tin diacetate

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Inadequate Study
Male Mice:	Negative
Female Mice:	Negative

TR-184 Bioassay of Nitrofen for Possible Carcinogenicity (CAS No. 1836-75-5)

Nitrofen, a substituted diphenyl ether, is one of several agricultural pesticides selected for bioassay by the National Cancer Institute because of a lack of carcinogenicity data.

A bioassay for the possible carcinogenicity of nitrofen was conducted using Fischer 344 rats and $B6C3F_1$ mice. Nitrofen was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. Twenty animals of each sex and species were placed on test as controls. The high and low dietary concentrations of nitrofen were 6000 and 3000 ppm for both species. The compound was administered to rats and mice for 78 weeks, followed by a period of no compound administration of 26 weeks for rats and 13 weeks for mice.

There were no significant positive associations between the concentrations of nitrofen administered and mortality in rats or mice of either sex. Adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. Dose-related mean body weight depression, relative to controls, was observed for males and females of both species, indicating that the concentrations of nitrofen administered to the animals in this bioassay may have approximated the maximum tolerated concentrations.

None of the statistical tests for any site in rats of either sex indicated a significant positive association between compound administration and tumor incidence. There was a significant positive association between the concentration of nitrofen administered and the incidences of hepatocellular carcinomas in mice of both sexes.

In another bioassay of nitrofen for possible carcinogenicity, the compound was found to induce hepatocellular carcinomas in $B6C3F_1$ mice of both sexes and hemangiosarcomas of the liver in male $B6C3F_1$ mice. In addition, adenocarcinomas of the pancreas were induced in female Osbourne-Mendel rats.

Under the conditions of this bioassay, dietary administration of nitrofen was carcinogenic to $B6C3F_1$ mice, causing hepatocellular carcinomas in both sexes. There was no evidence for carcinogenicity in Fischer 344 rats.

Synonyms: 2,4-dichloro-1-(4-nitrophenoxy)-benzene, 2,4-dichlorophenyl-p-nitrophenyl ether, nitrophene, Tok E-25, Nip

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative
Male Mice:	Positive
Female Mice:	Positive

Note: Nitrofen was previously studied by administration in feed to Osborne-Mendel rats and B6C3F$_1$ mice (See TR-26, reported 1979).

TR-185 Bioassay of Styrene for Possible Carcinogenicity (CAS No. 100-42-5)

Styrene, a widely used intermediate in the manufacture of plastics, elastomers, and resins, was selected for bioassay by the National Cancer Institute because of the widespread use of this compound and a lack of adequate carcinogenicity data.

A bioassay for the possible carcinogenicity of styrene was conducted using Fischer 344 rats and B6C3F$_1$ mice. Styrene was administered by gavage to groups of 50 male and 50 female animals of each species. Forty rats of each sex and twenty mice of each sex were placed on test as vehicle controls. The high, medium, and low dosages of styrene administered to rats were, respectively, 2,000, 1,000, and 500 mg/kg. The high and low dosages administered to mice were 300 and 150 mg/kg, respectively. The compound was administered for 78 weeks to high and medium dose rats, for 103 weeks to low dose rats, and for 78 weeks to mice. The period of compound administration was followed by an observation period of 27 weeks for high and medium dose rats, 1 week for low dose rats, and 13 weeks for mice.

Mortality among male and female high dose rats was significantly higher than that among their respective vehicle controls. In response to this elevated and early mortality, an additional dosed group of each sex was included in the chronic bioassay. No significant positive association was apparent between dosage and mortality among any other dosed rat groups. For mice, there was a significant positive association between mortality and the dosages of styrene administered to males, but not to females. Adequate numbers of animals in all groups, except for the high dose male and female rats, survived sufficiently long to be at risk from late-developing tumors. Slight dose-related mean body weight depression was apparent when male rats and female mice were compared to their respective vehicle controls, indicating that the dosages administered to these animals during the chronic bioassay may have approximated the maximum tolerated dosages. There was no distinct depression in mean body weight when dosed female rats and dosed male mice were compared to their respective vehicle controls. However, since there was significant accelerated mortality among high dose female rats, it is possible that the dosage administered to the medium dose female rats may have exceeded the maximum tolerated dosage.

In male mice, there was a significant positive association between styrene dosage and the incidences of a combination of adenomas and carcinomas of the lung. This finding was supported by the high dose to control Fischer exact comparison. However, the variation of the incidence of these neoplasms in historical control male mice at this laboratory does not permit a firm conclusion of carcinogenicity. There was no significant difference between tumor incidence at any other site in male mice, or at any site in rats or female mice, when dosed groups were compared to vehicle controls.

The findings of an increased incidence of a combination of adenomas and carcinomas of the lung provided suggestive evidence for the carcinogenicity of styrene in male B6C3F$_1$ mice. However, it is concluded that, under the conditions of this bioassay, no convincing evidence for the carcinogenicity of the compound was obtained in Fischer 344 rats or B6C3F$_1$ mice of either sex.

Synonyms: ethenylbenzene; vinylbenzene; vinylbenzol; styrolene; styrol; styrole; styropol; styropor; styron; cinnamene; cinnamol; phenethylene; phenylethylene; phenylethene

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative
Male Mice:	Equivocal
Female Mice:	Negative

TR-186 Bioassay of 4,4'-Methylenebis-(N,N-dimethyl)benzeneamine for Possible Carcinogenicity (CAS No. 101-61-1)

4,4'-Methylenebis(N,N-dimethyl)benzeneamine, a bicyclic aromatic amine and an intermediate in dye manufacture, was selected for bioassay by the National Cancer Institute because of a high incidence of bladder cancer observed among dye manufacturing industry workers.

A bioassay for the possible carcinogenicity of 4,4'-methylenebis-(N,N-dimethyl)benzeneamine was conducted using Fischer 344 rats and B6C3F$_1$ mice. 4,4'-Methylenebis-(N,N-dimethyl)benzeneamine was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. Twenty animals of each sex and species were placed on test as controls. The high and low dietary concentrations of 4,4'-methylenebis-(N,N-dimethyl) benzeneamine were, respectively, 750 and 375 ppm for rats and 2500 and 1250 ppm for mice. The compound was administered for 59 weeks to rats and for 78 weeks to mice. The period of compound administration was followed by an observation period of 45 weeks for rats and 13 weeks for mice.

There were no significantly positive associations between the concentrations of 4,4'-methylenebis-(N,N-dimethyl)benzeneamine administered and mortality among rats or mice of either sex. Adequate numbers of animals survived sufficiently long to be at risk from late-developing tumors. There was slight dose-related mean body weight depression among female rats, the mean body weight of high dose male rats was slightly less than that for controls, and the mean body weights of dosed mice were significantly lower than their controls, indicating that the concentrations of 4,4'-methylenebis-(N,N-dimethyl)benzeneamine administered to these animals in this bioassay may have approximated the maximum tolerated concentrations.

For both male and female rats, there was a significant positive association between the concentrations of 4,4'-methylenebis-(N,N-dimethyl)benzeneamine administered and the incidences of follicular-cell carcinomas of the thyroid (i.e., 1/18, 4/50, and 21/46 in the control, low dose, and high dose males, respectively; and 0/20, 3/46, and 23/45 in the control, low dose, and high dose females, respectively). The high dose to control Fischer exact comparisons were also significant for each sex.

Liver neoplasms were observed among male and female mice. There were elevated incidences of hepatocellular adenomas in dosed mice when compared to controls (i.e., 2/20, 3/50, and 16/48 in control, low dose, and high dose males, respectively; and 1/19, 18/49, and 22/48 in control, low dose, and high dose females). The incidences of hepatocellular carcinomas in dosed mice did not differ greatly from those in controls (i.e., 3/20, 9/50, and 6/48 in control, low dose, and high dose males, respectively; and 0/19, 1/49, and 1/48 in control, low dose, and high dose females). Among both sexes of mice, there was a significant positive association between the concentrations of the chemical administered and the incidences of a combination of hepatocellular adenomas and hepatocellular carcinomas. For male mice, the Fischer exact comparisons were not significant; however, for females, both the high dose to control and the low dose to control comparisons were significant.

In both sexes of both species nonneoplastic proliferative lesions of the thyroid occurred in dosed animals but not in any of the controls.

Under the conditions of this bioassay, 4,4'-methylenebis-(N,N-dimethyl)benzeneamine was carcinogenic in Fischer 344 rats, inducing thyroid follicular-cell carcinomas in both males and females. Administration of the compound was carcinogenic in female $B6C3F_1$ mice, inducing liver neoplasms. There was no conclusive evidence that 4,4'-methylenebis-(N,N-dimethyl) benzeneamine was carcinogenic in male $B6C3F_1$ mice.

Synonyms: 4,4'-methylenebis(N,N-dimethyl)aniline; tetramethyldiaminodiphenylmethane; 4,4'-bis(dimethylamino) diphenylmethane; Tetra base; Methane base; Michler's base; Michler's hydride; Michler's methane

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Positive
Female Rats:	Positive
Male Mice:	Equivocal
Female Mice:	Positive

TR-187 Bioassay of 5-Chloro-o-toluidine for Possible Carcinogenicity (CAS No. 95-79-4)

5-Chloro-o-toluidine, an aromatic amine and dye intermediate, was selected for bioassay by the National Cancer Institute because of the high incidence of bladder cancer observed among dye manufacturing industry workers.

A bioassay for the possible carcinogenicity of 5-chloro-o-toluidine was conducted using Fischer 344 rats and $B6C3F_1$ mice. 5-Chloro-o-toluidine was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. Twenty animals of each sex and species were placed on test as controls. The high and low dietary concentrations of 5-chloro-o-toluidine were 5,000 and 2,500 ppm for rats and 4,000 and 2,000 ppm for mice. The compound was administered in the diet for 78 weeks, followed by an observation period of 26 weeks for rats and 13 weeks for mice.

There were significant positive associations between the concentrations of 5-chloro-o-toluidine administered and mortality among male and female mice, but not among rats of either sex. Adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. Distinct mean body weight depression was apparent when dosed female rats and dosed mice of both sexes were compared to their controls, indicating that the concentrations administered to these animals in this bioassay may have approximated the maximum tolerated concentrations. Since no mean body weight depression, relative to controls, no significantly accelerated mortality, and no signs of toxicity other than fatty metamorphosis of the liver were associated with administration of 5-chloro-o-toluidine to male rats, it is possible that these animals may have been able to tolerate a higher dietary concentration of the compound.

There was a significant positive association between the concentration of 5-chloro-o-toluidine administered to male rats and the incidence of adrenal pheochromocytomas in these animals; however, neither of the Fischer comparisons was significant. None of the other statistical tests for tumors at any site in male and female rats indicated a significant positive association between dosage and incidence.

In mice of both sexes there were significant positive associations between concentration administered and the incidence of hemangiosarcomas. In addition, the high dose to control Fischer exact comparisons for both sexes were significant. The Cochran-Armitage tests were also significant and positive for the incidences of hepatocellu-

lar carcinomas in both sexes of mice. For males and females the high dose to control Fischer exact comparisons were significant, and for females the low dose to control comparison was also significant.

Under the conditions of this bioassay, 5-chloro-o-toluidine was carcinogenic to B6C3F$_1$ mice, inducing hemangiosarcomas and hepatocellular carcinomas in both males and females. There was no conclusive evidence of the carcinogenicity of the compound in Fischer 344 rats.

Synonyms: 5-chloro-2-methylbenzeneamine; p-chloro-o-aminotoluene; 4-chloro-2-aminotoluene; 2-amino-4-chlorotoluene; o-amino-p-chlorotoluene; 5-chloro-2-methylaniline; 2-methyl-5-chloroaniline; 1-amino-2-methyl-5-chlorobenzene; 1-amino-3-chloro-6-methylbenzene; Fast Red KB Base; Azogene Fast Red KB; Brentamine Fast Red KB Base; Naphthosol Fast Red Base; Naphthanil Red KB Base

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative
Male Mice:	Positive
Female Mice:	Positive

TR-188 Sodium Iodomethanesulfonate (CAS: 126-31-8)

Data considered to be inconclusive and not reportable; no Technical Report issued.

TR-189 Bioassay of p-Chloroaniline for Possible Carcinogenicity (CAS No. 106-47-8)

p-Chloroaniline, a dye and chemical intermediate, was selected for bioassay by the National Cancer Institute because of the high incidence of bladder cancer observed among dye manufacturing industry workers.

A bioassay for the possible carcinogenicity of p-chloroaniline was conducted using Fischer 344 rats and B6C3F$_1$ mice. p-Chloroaniline was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. Twenty animals of each sex and species were placed on test as controls. The high and low dietary concentrations of p-chloroaniline were, respectively, 500 and 250 ppm for rats and 5000 and 2500 ppm for mice. The compound was administered in the diet for 78 weeks, followed by an observation period of 24 weeks for rats and 13 weeks for mice.

There were no significant positive associations between the dietary concentrations of p-chloroaniline administered and mortality in female rats or in mice of either sex; however, there was a significantly positive association between concentration and mortality in male rats. Adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. Mean body weight depression, in relation to controls, was observed in high dose female rats and dosed mice of both sexes, indicating that the concentration of p-chloroaniline administered to these animals may have approximated the maximum tolerated concentrations. Although splenic lesions were observed in male rats, no mean body weight depression relative to controls was associated with administration of p-chloroaniline to these animals. Therefore, it is possible that these animals may have been able to tolerate a higher dietary concentration of the compound.

The only neoplastic lesions found that might be related to administration of the compound were mesenchymal tumors in the spleens of male rats and hemangiomatous tumors in mice. In male rats, there was a significant positive association between compound administration and the incidences of fibroma or fibrosarcoma of the spleen. The incidences of these tumors were not significantly elevated when compared to those in control rats, but the rarity of these tumors in male Fischer 344 rats (0/360 in historical male control rats in this laboratory) strongly suggests a chemically related effect. In addition, three sarcomas of other types were found in high dose male rats. In mice of both sexes, hemangiomas and hemangiosarcomas were found at elevated incidences, when compared to control mice, in the spleen, liver, kidney, and multiple body sites. The increased incidences in dosed mice were statistically related to dose but were not statistically significant when compared directly to matched control animals. In comparison to historical control data, the incidences of hemangiomatous tumors in the dosed mice were elevated, but not greatly. The evidence was considered insufficient to conclusively relate the hemangiomatous tumors in mice to compound administration. Nonneoplastic proliferative and chronic inflammatory lesions were also found in the spleens of dosed rats and mice.

The findings of small numbers of fibromas and sarcomas in the spleens of male rats was considered strongly suggestive of carcinogenicity because of the rarity of these tumors in the spleens of control rats. Hemangiomatous tumors in dosed mice may also have been associated with administration of p-chloroaniline. However, it is concluded that, under the conditions of this bioassay, sufficient evidence was not found to establish the carcinogenicity of p-chloroaniline for Fischer 344 rats or B6C3F$_1$ mice.

Synonyms: 4-chlorobenzeneamine; 4-chlorophenylamine; 4-chloroaniline; 4-CA; 1-amino-4-chlorobenzene

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Equivocal
Female Rats:	Negative
Male Mice:	Equivocal
Female Mice:	Equivocal

TR-190 Bioassay of p-Nitrosodiphenylamine for Possible Carcinogenicity (CAS No. 156-10-5)

p-Nitrosodiphenylamine is used to accelerate the vulcanization of rubber. It is also used as an intermediate in the manufacture of dyes and pharmaceutical compounds and as an inhibitor of polymerization during the production of vinyl monomers such as styrene.

A bioassay for the possible carcinogenicity of p-nitrosodiphenylamine was conducted using Fischer 344 rats and $B6C3F_1$ mice. p-Nitrosodiphenylamine was administered in the feed, at either of two concentrations, to groups of 50 male and female animals of each species. Twenty animals of each sex and species were placed on test as controls. The high and low dietary concentrations of p-nitrosodiphenylamine were, respectively, 5000 and 2500 ppm for rats. The high and low time-weighted average concentrations for mice were 9000 and 4254 ppm, respectively. The compound was administered for 78 weeks to rats, for 50 weeks to high dose mice and for 57 weeks to low dose mice. The period of compound administration was followed by an observation period of 27 weeks for rats and 35 weeks for mice.

There were significant positive associations between the concentrations of p-nitrosodiphenylamine administered and mortality among male and female mice, but not for rats of either sex. Although 19/50 high dose male mice and 21/50 high dose female mice died before week 52, adequate numbers of mice and rats survived sufficiently long to be at risk from late-developing tumors. The toxicity observed in mice and the dose-related mean body weight depression apparent in male and female rats indicated that the concentrations of p-nitrosodiphenylamine administered to these animals in this bioassay may have approached or exceeded the maximum tolerated concentrations.

In male rats, there was a significant positive association between concentration administered and the incidence of a combination of hepatocellular carcinomas and neoplastic nodules. In addition, both the high dose to control and the low dose to control Fischer exact comparisons were significant. There was also a significant positive association between concentration administered and the incidence of alveolar/bronchiolar adenomas in male rats; however, neither of the Fischer exact comparisons were significant. There were no positive, significant statistical tests for tumor incidence at any site in female rats.

Due to the large number of early deaths among high dose mice of both sexes, the statistical conclusion concerning carcinogenicity was based on comparisons between the low dose and control groups. The incidence of hepatocellular carcinomas was significantly higher among the low dose males than among their controls. Although hepatocellular neoplasms were observed in dosed females, there were no tumors occurring with a statistically increased incidence when low dose females were compared to their controls.

Under the conditions of this bioassay, p-nitrosodiphenylamine was carcinogenic when administered in the diet to male $B6C3F_1$ mice, causing hepatocellular carcinomas. The chemical was also carcinogenic in male Fischer 344 rats, causing liver neoplasms. No evidence was provided for the carcinogenicity of p-nitrosodiphenylamine in female $B6C3F_1$ mice or in female Fischer 344 rats.

Synonyms: 4-nitroso-N-phenylbenzeneamine; 4-nitrosodiphenylamine; p-nitroso-N-phenylaniline; TKB

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Positive
Female Rats:	Negative
Male Mice:	Positive
Female Mice:	Negative

TR-191 Bioassay of Technical Grade Bis(2-chloro-1-methylethyl) ether for Possible Carcinogenicity (CAS No. 108-60-1)

Bis(2-chloro-1-methylethyl) ether is a beta-haloether and a byproduct of propylene oxide and propylene glycol manufacture.

A bioassay of technical grade bis(2-chloro-1-methylethyl) ether for possible carcinogenicity was conducted by administering the test chemical by gavage to F344 rats.

Groups of 50 rats of each sex were administered a solution of bis(2-chloro-1-methylethyl) ether in corn oil 5 days per week at either 100 or 200 mg/kg/day for 103 weeks. Vehicle controls consisted of groups of 50 rats of each sex that were administered the corn oil alone. Untreated-control groups of the same size were also used. All surviving rats were killed at week 104 or 105.

Mean body weights of the dosed groups of male and female rats were lower than those of the corresponding vehicle-control groups throughout most of the study and were dose related. Similarly, survivals of the high-dose males and of both the high- and low-dose females were lower than those of the corresponding vehicle controls and were dose related. Almost all animals in the high-dose groups died by the end of the bioassay.

No tumors occurred in the dosed groups of rats of either sex at incidences that were significantly higher than those of the vehicle-control groups.

It is concluded that under the conditions of this bioassay, the technical-grade test material, bis(2-chloro-1-methylethyl) ether, was not carcinogenic for F344 rats of either sex.

Synonym: bis(2-chloro-isopropyl) ether

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative

Note: Bis(2-chloro-1-methylethyl)ether was subsequently tested in B6C3F$_1$ mice by gavage (See TR-239, reported 1982).

TR-192 Bioassay of Malathion for Possible Carcinogenicity (CAS No. 121-75-5)

Malathion is an organophosphate insecticide considered to be suitable as a substitute for certain uses of DDT. U.S. consumption in 1974 was 16 million pounds, surpassing that of all other organophosphate insecticides except methyl parathion. Household applications accounted for approximately 10% of that volume.

A bioassay of malathion for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats.

Groups of 49 or 50 rats of each sex were fed diets containing 2,000 or 4,000 ppm malathion for 103 weeks and were then observed for an additional 2 or 3 weeks. Matched controls consisted of 50 untreated rats of each sex. All surviving rats were killed at 105 or 106 weeks.

No tumors occurred in the dosed groups of rats of either sex at incidences that could be related clearly to administration of the test chemical. Compound-related toxic effects were not observed in female rats at the doses used, but in males decreased mean body weights, increased mortality, gastritis, and gastric ulcers were dose related.

It was concluded that under the conditions of this bioassay, malathion was not carcinogenic in male or female rats, but the females may not have received a maximum tolerated dose.

Synonym: S-(1,2-bis(ethoxycarbonyl)-ethyl) *O,O*-dimethylphosphorodithioate

Report Date: 1979

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative

Note: Malathion was previously tested in Osborne-Mendel rats and B6C3F$_1$ mice administered in feed (See TR-24, reported 1978).

TR-193 Bioassay of Resperine for Possible Carcinogenicity (CAS No. 50-55-5)

A bioassay for possible carcinogenicity of resperine, an antihypertensive drug for human use, was conducted by administering the test chemical in feed to F344 rats and B6C3F$_1$ mice.

Groups of 50 rats and 50 mice of each sex were administered resperine at two doses, 5 ppm and 10 ppm, for 103 weeks and then observed for an additional 2 weeks. Matched controls consisted of groups of 50 untreated rats and 50 untreated mice of each sex. All surviving animals were killed and necropsied at the end of 104 or 105 weeks.

The significant effects that could be related to administration of resperine at the doses used were decreased body weight and increased tumor formation in dosed male rats and in mice of both sexes. Dosed male rats had an increased incidence of adrenal medullary pheochromocytomas. Among dosed mice, some males developed undifferentiated carcinomas of the seminal vesicles, which rarely occur in control mice, and females had an increased incidence of mammary cancer.

It was concluded that, under the conditions of the bioassay, resperine was carcinogenic in male rats and in mice of both sexes, producing three different kinds of cancers. Resperine was not carcinogenic for female rats, but they may not have received a high enough dose for maximum test sensitivity.

Report Date: November 1982

Levels of Evidence of Carcinogenicity:

Male Rats:	Positive
Female Rats:	Negative
Male Mice:	Positive
Female Mice:	Positive

TR-194 Bioassay of Selenium Sulfide (Gavage) for Possible Carcinogenicity (CAS No. 7446-34-6)

Selenium sulfide is an ingredient in dandruff shampoos used in concentrations of 1% in products sold over-the-counter and 2.5% in products which are available by prescription only. Prescription shampoos have been shown in clinical studies to be of therapeutic value against dandruff. An antimitotic mechanism of action is suggested by data showing that selenium sulfide decreases the rate of incorporation of radioactively labeled thymidine into the DNA of dermal epithelial cells. Approximately 200 kg of selenium sulfide is estimated to be used annually for this purpose.

A bioassay of selenium sulfide for possible carcinogenicity was conducted by administering this substance by gavage to F344 rats and B6C3F$_1$ mice.

Groups of 50 rats and 50 mice of each sex were administered selenium sulfide suspended in 0.5% aqueous carboxymethylcellulose 7 days per week for 103 weeks at either 3 or 5 mg/kg/day for rats and 20 or 100 mg/kg/day for mice. As vehicle controls, groups of 50 rats and 50 mice of each sex were administered only the 0.5% aqueous carboxymethylcellulose. Similar groups of untreated controls also were used. All surviving rats and mice were killed and necropsied at week 104 or 105.

The significant effects that could be related to administration of selenium sulfide at the doses used were

decreased body weight and increased tumor formation in female mice and in rats of each sex. Dosed rats and female mice had an increased incidence of hepatocellular carcinomas and adenomas. Dosed female mice also had an increased incidence of alveolar/bronchiolar carcinomas and adenomas.

Under the conditions of this bioassay, selenium sulfide was carcinogenic for F344 rats and female $B6C3F_1$ mice, including hepatocellular carcinomas in male and female rats and female mice and alveolar/bronchiolar carcinomas and adenomas in female mice. Selenium sulfide was not carcinogenic for male mice; but they have been able to tolerate higher doses.

Report Date: August 1980

Levels of Evidence of Carcinogenicity:

Male Rats:	Positive
Female Rats:	Positive
Male Mice:	Negative
Female Mice:	Positive

Note: Selenium sulfide was subsequently tested in ICR Swiss mice administered dermally (See TR-197, reported 1980).

TR-195 Bioassay of Fluometuron for Possible Carcinogenicity (CAS No. 2164-17-2)

Fluometuron is a phenylurea herbicide used in agriculture to control broad-leaved and grass weeds in cotton and sugarcane fields. The area of heaviest use is the Mississippi delta. Applications of low concentrations selectively kill weeds.

A bioassay of the phenylurea herbicide fluometuron for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and $B6C3F_1$ mice.

Groups of 50 rats of each sex were fed diets containing 125 or 250 ppm of fluometuron for 103 weeks, and groups of 50 mice of each sex were fed diets containing 500 or 1,000 ppm of fluometuron for 103 weeks. Matched controls consisted of groups of 50 untreated rats and 25 untreated mice of each sex. All surviving animals were killed at 103 to 105 weeks.

Splenomegaly observed in rats in the subchronic studies influenced selection of the doses for the chronic study; however, no splenic effects were observed in the chronic study.

Mean body weights of the dosed groups of male and female rats and mice were essentially the same as those of the corresponding control groups. Survival of dosed groups of rats and mice was similar to that of the corresponding control groups. Similarities between mean body weights and survival between dosed and control animals in the chronic study suggest that these animals could have tolerated higher doses.

The only possible carcinogenic effects from compound administration were in male mice. Incidences of hepatocellular carcinomas or adenomas in male mice were dose related, and the incidence in the high-dose group was marginally higher than that in the corresponding matched controls or pooled controls from concurrent studies.

Under the conditions of this bioassay, fluometuron was not carcinogenic for F344 rats or for female $B6C3F_1$ mice. Equivocal results were obtained for male $B6C3F_1$ mice which may have had an increased incidence of hepatocellular tumors. Because of the equivocal findings and because both rats and mice may have been able to tolerate higher doses, it is concluded that additional testing of fluometuron for carcinogenicity is warranted.

Synonym: 1,1-dimethyl-3-(a,a,a-trifluoro-m-tolyl) urea

Report Date: August 1980

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative
Male Mice:	Equivocal
Female Mice:	Negative

TR-196 Bioassay of Cinnamyl Anthranilate for Possible Carcinogenicity (CAS No. 87-29-6)

A bioassay of cinnamyl anthranilate (a synthetic flavoring agent) for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and $B6C3F_1$ mice.

Groups of 50 rats and 50 mice of each sex were fed the test chemical in diets containing 15,000 or 30,000 ppm for 103 weeks and then observed for an additional 2 or 3 weeks. Controls consisted of groups of 50 untreated rats and 50 untreated mice of each sex. All surviving animals were killed and necropsied at 105 to 107 weeks.

Mean body weights of the dosed male and female rats and mice were lower than those of the corresponding controls throughout the bioassay, and weight decrements were dose related. Mortality in rats and mice of either sex was not affected by administration of the test chemical.

In male rats, adenocarcinomas or adenomas of the renal cortex and acinar-cell carcinomas or adenomas of the pancreas were found in low incidences in dosed rats but not in control rats. In direct comparisons with matched control groups, the incidences of these tumors were not significantly increased; however, because these tumors rarely occur spontaneously in aging F344 rats, they were considered to be related to compound administration. Similar pancreatic or renal tumors have not been detected among 634 historical-control male F344 rats at the same laboratory.

In the female rats, no tumors occurred at incidences that could be clearly related to the administration of the test chemical.

In both male and female mice, the incidences of hepatocellular carcinomas or adenomas were dose

related ($P<0.001$) and significant ($P\leq 0.001$) in direct comparisons of dosed and control groups.

It was concluded that under the conditions of this bioassay cinnamyl anthranilate was carcinogenic for male and female $B6C3F_1$ mice, inducing increased incidences of hepatocellular carcinomas or adenomas. The test chemical was also carcinogenic for male F344 rats, inducing low incidences of acinar-cell carcinomas or adenomas of the pancreas and adenocarcinomas or adenomas of the renal cortex. Cinnamyl anthranilate was not carcinogenic for female F344 rats.

Synonyms: 2-aminobenzoic acid, 3-phenyl-2-propenyl ester; anthranilic acid, cinnamyl ester

Report Date: August 1980

Levels of Evidence of Carcinogenicity:

Male Rats:	Positive
Female Rats:	Negative
Male Mice:	Positive
Female Mice:	Positive

TR-197 Bioassay of Selenium Sulfide (Dermal Study) for Possible Carcinogenicity (CAS No. 7446-34-6)

Selenium is an essential nutrient, and various selenium compounds have industrial and medical uses.

The possible carcinogenicity of selenium sulfide (a component in shampoos) was investigated by applying a suspension of this substance to the skin of ICR Swiss mice. Groups of 50 mice of each sex were treated by applying 0.5 mg or 1.0 mg selenium sulfide three times a week for 86 weeks to a clipped 2- x 3-cm dorsal surface. The selenium sulfide was suspended in 0.05 ml saline solution containing 0.5% carboxymethylcellulose.

Mean body weights of all dosed and control groups were comparable throughout the study. Amyloidosis, previously reported as a cause of death in Swiss mice, was a factor in the deaths of most treated and control mice after 1 year, and the study was terminated after 88 weeks when the majority of animals in all dosed and control groups had died.

Under the conditions of this bioassay, dermal application of selenium sulfide did not produce a carcinogenic effect in ICR Swiss mice, but the study was limited by the relatively short lifespan of this strain of mouse.

Report Date: August 1980

Levels of Evidence of Carcinogenicity:

Male Mice:	Negative
Female Mice:	Negative

Note: Selenium Sulfide was previously tested in F344 and $B6C3F_1$ mice administered by gavage (See TR-194, reported 1980).

TR-198 Bioassay of a Mixture of 1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin and 1,2,3,7,8,9-Hexachlorodibenzo-p-dioxin (Gavage) for Possible Carcinogenicity (CAS No. 57653-85-7, CAS No. 19408-74-3)

Hexachlorodibenzo-p-dioxins (HCDD) are formed during the manufacture of certain chlorophenols. They have been found in trichlorophenol, tetrachlorophenol, and pentachlorophenol and in the chlorophenol-derived herbicides, 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). From 1967 to 1970, the concentration of HCDD in commercial pentachlorophenol ranged from 0.03 to 38 ppm. Since then, HCDD levels in pentachlorophenol have been less than 1 ppm.

A bioassay of a mixture of 1,2,3,6,7,8- and 1,2,3,7,8,9-hexachlorodibenzo-p-dioxin (HCDD) for possible carcinogenicity was conducted by administering the test material by gavage to Osborne-Mendel rats and $B6C3F_1$ mice for 104 weeks.

Fifty rats and 50 mice of each sex were administered HCDD suspended in a vehicle of 9:1 corn oil-acetate 2 days per week for 104 weeks at doses of 1.25, 2.5, or 5 μg/kg/wk for rats and male mice and 2.5, 5, or 10 μg/kg/wk for female mice. Seventy-five rats and 75 mice of each sex served as vehicle controls. In addition, one untreated control group containing 25 rats and 25 mice of each sex was present in the HCDD treatment room, and one untreated control group containing 25 rats and 25 mice of each sex was present in the vehicle control room. All surviving animals were killed at 105 to 108 weeks.

In rats, a dose-related depression in mean body weight gain became evident in the males after week 68 of the bioassay and in the females after week 33. In mice, the mean body weight gain in the dosed groups was comparable with that of the vehicle control groups. No other toxic clinical signs were reported in either the rats or the mice. Administration of HCDD had no adverse effect on the survival of either species.

In male rats, hepatocellular carcinomas or neoplastic nodules occurred at low incidences that were dose related ($P=0.003$). In a direct comparison, the incidence of these tumors in the high-dose group was higher ($P=0.022$) than that in the corresponding vehicle-control groups, but the Bonferroni requirement of $P=0.017$ for the multiple comparison of three dosed groups with a control group was not met.

In female rats, hepatocellular carcinomas, adenomas, or neoplastic nodules occurred at incidences that were dose related ($P<0.001$), and in direct comparisons the incidences of these tumors in the mid- and high-dosed groups were significantly higher ($P=0.006$ and $P<0.001$, respectively) than those in the corresponding vehicle-control group.

In male mice, hepatocellular carcinomas or adenomas occurred at incidences that were dose related ($P=0.001$), and in a direct comparison the incidence of these tumors in the high-dose group was significantly higher ($P=0.001$) than that in the corresponding vehicle-control group.

In female mice, hepatocellular carcinomas or adenomas occurred at incidences that were dose-related ($P = 0.002$), and the incidence of these tumors in the high-dose group was significantly higher ($P = 0.004$) than that in the corresponding vehicle-control group.

Complex nonneoplastic toxic liver lesions were seen in all dosed groups of rats and mice. Compound-associated hyperplastic lesions of the lung were also found in both male and female rats.

Under the conditions of this bioassay, HCDD administered by gavage was carcinogenic, causing increased incidences of hepatocellular carcinomas or neoplastic nodules in female Osborne-Mendel rats and inducing hepatocellular carcinomas and adenomas in male and female $B6C3F_1$ mice. HCDD was not demonstrated to be carcinogenic for male rats.

Synonym: HCDD

Report Date: August 1980

Levels of Evidence of Carcinogenicity:

Male Rats:	Equivocal
Female Rats:	Positive
Male Mice:	Positive
Female Mice:	Positive

Note: 1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin and 1,2,3,7,8.9-Hexachlorodibenzo-p-dioxin were subsequently tested in Swiss-Webster mice administered dermally (See TR-202, reported 1980).

TR-199 Bioassay of Selsun® for Possible Carcinogenicity

A bioassay of Selsun® for possible carcinogenicity was conducted by applying this substance dermally to ICR Swiss mice. Selsun®, an antidandruff shampoo, contains 2.5% selenium sulfide.

Groups of 50 mice of each sex were exposed to 0.05 ml of 25% or 50% Selsun® in distilled water three times a week on a 2- x 3-cm clipped dorsal surface. Vehicle controls consisted of 50 mice of each sex that were clipped and treated with distilled water. Untreated controls consisted of 50 mice of each sex that were only clipped. Surviving mice were killed and necropsied at week 88.

Mean body weights of untreated control, vehicle control, low-dose, and high-dose groups were comparable throughout the bioassay. Amyloidosis was a factor in the deaths of most animals after 1 year. In male mice, alveolar/bronchiolar carcinomas or adenomas occurred with a dose-related trend that was significant ($P = 0.008$). The result of the Fisher exact test comparing the incidence in the high-dose group with that in the vehicle controls is also significant, but the incidence of the high-dose group, when compared with that of the untreated controls, is not significant.

Under the conditions of this bioassay, dermal application of Selsun® was not carcinogenic for ICR Swiss mice. The study was limited, however, by the relatively short lifespan of this strain of mouse.

Report Date: August 1980

Levels of Evidence of Carcinogenicity:

Male Mice:	Negative
Female Mice:	Negative

TR-200 Bioassay of 2,6-Toluenediamine Dihydrochloride for Possible Carcinogenicity (CAS No. 15481-70-6)

2,6-Toluenediamine is used as an intermediate in the production of dyes for furs and textiles, and of flexible polyurethane foams and elastomers. A bioassay of 2,6-toluenediamine dihydrochloride for possible carcinogenicity was conducted by feeding diets containing the test chemical to F344 rats and $B6C3F_1$ mice.

Groups of 50 rats of each sex were fed the test chemical at two doses, 250 or 500 ppm, for 103 weeks and observed for 1 additional week. Groups of 50 mice of each sex were fed the test chemical at two doses, 50 or 100 ppm, for 103 weeks and then observed for 1 additional week. Groups of 50 untreated rats and 50 untreated mice of each sex were used as matched controls. All surviving animals were killed and necropsied at 104 weeks.

Weight gain depression was less than 10% for dosed groups of male rats and male and female mice, when compared with controls. Mean body weight gain was depressed 17% in low-dose female rats and 27% in high-dose female rats. Mortality was not increased in rats or mice of either sex by the test chemical. No clinical evidence indicated that mice of either sex received a maximum tolerated dose of the compound.

In male rats, islet-cell adenomas of the pancreas and neoplastic nodules or carcinomas of the liver occurred in dose-related trends that were significant using the Cochran-Armitage test ($P = 0.025$ and $P = 0.037$, respectively). The results of the Fisher exact test were not significant for either lesion. The occurrences of tumors in dosed female rats were not significantly different from those in control rats.

Significant results in the negative direction were observed in the incidences of C-cell tumors of the thyroid in male rats and of fibroadenomas of the mammary gland in female rats.

In male mice, in the low-dose group, lymphomas occurred at an incidence significantly higher ($P = 0.046$) than that of the corresponding control group; however, the incidence was not significant when the Bonferroni criterion for multiple comparison was used.

The occurrence of hepatocellular carcinomas in female mice was dose related, but the result of the Fisher exact test comparing the incidence in the high-dose group with that in the controls was not significant.

It was concluded that, under the conditions of the bioassay, 2,6-toluenediamine dihydrochloride was not

carcinogenic for male and female F344 rats or for male and female $B6C3F_1$ mice.

Report Date: August 1980

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative
Male Mice:	Negative
Female Mice:	Negative

TR-201 Carcinogenesis Bioassay of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (CAS No. 1746-01-6) in Swiss-Webster Mice (Dermal Study)

2,3,7,8-Tetrachlorodibenzo-p-dioxin occurs as a highly toxic impurity found in herbicides containing 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and 2,4,5-T derivatives, as well as in other chemicals synthesized using 2,4,5-trichlorophenol.

The herbicide 2,4,5-T has been marketed in the United States since 1948. Production increased sharply between 1960 and 1970 when a 1:1 mixture of 2,4,5-T and 2,4-dichlorophenoxyacetic acid (2,4-D) was used as a defoliant in Vietnam under the names of "herbicide agent orange, herbicide orange, agent orange, and orange". During this 10-year period, about 106 million pounds of 2,4,5-T were sprayed.

A carcinogenesis bioassay was conducted by applying an acetone suspension of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) to the clipped backs of 30 male and female Swiss-Webster mice 3 days per week for 99 or 104 weeks. Similar groups were pretreated with 1 application of 50 μg dimethylbenzanthracene (DMBA) in 0.1 ml acetone 1 week before TCDD administration began. Female mice received 0.005 μg TCDD per application, and the male mice received 0.001 μg TCDD. As vehicle controls, 45 mice of each sex received 0.1 ml acetone three times per week. Thirty animals of each sex were used as untreated controls.

Throughout the bioassay, mean body weights of the male and female mice administered TCDD, or TCDD following DMBA, were essentially the same as those of the corresponding vehicle control group. Mean body weights of dosed and vehicle control groups of males were less than those of the untreated control group throughout the study; for the females, mean body weights were less than the untreated controls during the first 80 weeks.

In female mice, the incidences of fibrosarcoma in the integumentary system in dosed groups with TCDD were significantly ($P = 0.007$) higher than that in the corresponding controls (2/41, 5%; 8/27, 30%). An increase in the same tumor type, although not statistically significant ($P = 0.084$), was also observed in the male mice (3/42, 7%; 6/28, 21%).

In the DMBA-TCDD experiment, failure to have included groups skin painted with only DMBA precluded interpretation of these results.

Under the conditions of this bioassay, 2,3,7,8-tetrachlorodibenzo-p-dioxin applied to the skin was not carcinogenic for male Swiss-Webster mice (the increase of fibrosarcomas in the integumentary system may have been associated with the skin application of TCDD). TCDD was carcinogenic for female Swiss-Webster mice causing fibrosarcomas in the integumentary system.

Synonyms: 2,3,7,8-TCDD; TCDD

Report Date: February 1982

Note: 2,3,7,8-Tetrachlorodibenzo-p-dioxin was subsequently tested in Osborne-Mendel rats and $B6C3F_1$ mice by gavage (See TR-209 reported 1982).

TR-202 Bioassay of a Mixture of 1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin and 1,2,3,7,8,9-Hexachlorodibenzo-p-dioxin (Dermal Study) for Possible Carcinogenicity (CAS No. 57653-85-7; CAS No. 19408-74-3)

Hexachlorodibenzo-p-dioxin (HCDD) is formed as a byproduct during the manufacture of certain chlorophenols and has been found in trichlorophenol, tetrachlorophenol, pentachlorophenol and in the chlorophenol-derived herbicides 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). From 1967 to 1970, the concentration of HCDD in commercial pentachlorophenol ranged from 0.03 to 38 ppm. Since then, HCDD levels in pentachlorophenol have been reduced to less than 1 ppm.

A bioassay of a mixture of 1,2,3,6,7,8- and 1,2,3,7,8,9-hexachlorodibenzo-p-dioxins (HCDD) for possible carcinogenicity was conducted by dermal application of a suspension of this substance to Swiss-Webster mice.

HCDD (0.01 μg) suspended in 0.1 ml acetone was applied to the backs of 30 mice of each sex 3 days per week for 104 weeks. During the first 16 weeks, doses were 0.005 μg HCDD per application. An additional 30 mice of each sex were pretreated with one application of 50 μg DMBA in 0.1 ml acetone 1 week before the initiation of the HCDD applications. As vehicle controls, 45 mice of each sex received 0.1 ml of acetone three times per week. Thirty animals of each sex served as untreated controls. Mean body weights of all test and vehicle control mice were comparable throughout the bioassay; mean body weights of untreated controls were higher than those of the test and vehicle-control groups.

In male mice, the incidence of alveolar/bronchiolar carcinomas in the group administered only HCDD was significantly higher ($P = 0.045$) than that in the vehicle-control group; however, the incidence was not significantly higher when compared with untreated controls.

In female mice, the incidences of fibrosarcomas of the skin were significantly higher (P = 0.044) in animals administered HCDD (both with and without pretreatment with DBMA) than in the untreated-control group; however, when the incidences were compared with those of the vehicle controls (relative risk = 3.037) the results were not significant.

Under the conditions of this bioassay, HCDD was not carcinogenic for male or female Swiss-Webster mice.

Synonym: HCDD

Report Date: August 1980

Levels of Evidence of Carcinogenicity:

Male Mice:	Negative
Female Mice:	Negative

Note: Hexachlorodibenzo-p-dioxin and 1,2,3,7,8,9-hexachlorodibenzo-p-dioxin were previously tested in Swiss-Webster mice administered dermally (See TR-198, reported 1980).

TR-203 Bioassay of Phenol for Possible Carcinogenicity (CAS No. 108-95-2)

Phenol ranked 38th in production among U.S. chemicals in 1978 with annual production of 2.38 billion pounds. Approximately 90% of the phenol produced is used in the manufacture of phenolic (phenol formaldehyde) resins, caprolactam, bisphenol A, alkyl phenol, and adipic acid. The remainder of the phenol is used to produce an assortment of end products, including salicylic acid, phenacetin, dyes, metal cleaners, disinfectants, antiseptics, photographic chemicals, wood preservatives (pentachlorophenol), paints, paint and varnish removers, and agricultural chemicals (2,4-D and parathion).

A bioassay of phenol to test for possible carcinogenicity was conducted by providing this substance in drinking water to F344 rats and $B6C3F_1$ mice. Groups of 50 rats and 50 mice of each sex were given drinking water containing 2,500 or 5,000 ppm phenol for 103 weeks. As matched controls, groups of 50 rats and 50 mice of each sex received tap water.

A dose-related depression in mean body weight gain occurred in rats and mice of each sex. Rats and mice given water containing phenol drank less than did the corresponding controls. A dose-related decrease in water consumption was observed for mice.

An increased incidence of leukemia or lymphomas was detected in male rats and may have been associated with the administration of phenol. Although the incidence of these tumors in the low-dose group was significantly higher than that in controls, the incidence in the high-dose group was not. Thus an association with administration of phenol was not established.

Under the conditions of this bioassay, phenol was not carcinogenic for either male or female F344 rats or male and female $B6C3F_1$ mice.

Report Date: August 1980

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative
Male Mice:	Negative
Female Mice:	Negative

TR-204 Bioassay of Benzoin for Possible Carcinogenicity (CAS No. 119-53-9)

A bioassay of benzoin for possible carcinogenicity was conducted by incorporating the test chemical in diets of F344 rats and $B6C3F_1$ mice. Benzoin is used as a photopolymerization catalyst, chemical intermediate, and flavor ingredient.

Groups of 50 male rats were fed diets containing 125 or 250 ppm benzoin for 104 weeks, and similar groups of female rats received feed containing 250 or 500 ppm. Groups of 50 mice of each sex were fed diets containing 2,500 or 5,000 ppm, benzoin for 104 weeks. Groups of 50 untreated rats and mice of each sex were used as matched controls. Rats and mice of either sex probably could have tolerated higher doses. An increased incidence of lymphomas or leukemia occurred in dosed male rats, but the observed dose-related trend was not statistically significant.

Mean body weights and clinical signs of low-dose, high-dose, and control male and female rats and male mice were comparable throughout the study, After week 44, mean body weights of dosed female mice were slightly lower (10% or less) than those of the controls.

The incidences of lymphomas that occurred in male mice varied with each dose but were not statistically significant when compared with those of matched controls.

Lymphomas or leukemias occurred in low-dose female mice at an incidence that was significant when compared with the matched controls. However, because the incidence of lymphomas or leukemias in the high-dose female mice was not significant, the occurrence of these tumors was not clearly related to administration of the test compounds.

Under the conditions of this bioassay, benzoin was not carcinogenic for F344 rats or $B6C3F_1$ mice.

Synonym: 2-hydroxy-1,2-diphenylethanone

Report Date: August 1980

Levels of Evidence of Carcinogenicity:

Male Rats:	Negative
Female Rats:	Negative
Male Mice:	Negative
Female Mice:	Negative

TR-205 Bioassay of 4,4'-Oxydianiline for Possible Carcinogenicity (CAS No. 101-80-4)

4,4'-Oxydianiline is used in the manufacture of high temperature resistant metal adhesives, molding and machine parts, and insulators. A bioassay of this chemical for possible carcinogenicity was conducted by feeding diets containing 200, 400, or 500 ppm of the test chemical to groups of 50 male or female F344 rats and 150, 300, or 800 ppm to groups of 50 male or female B6C3F$_1$ mice for 104 weeks. Matched controls consisted of 50 untreated rats and 50 untreated mice of each sex. All surviving animals were killed at 104 to 105 weeks.

A dose-related decrement in mean body weight gain was observed for all groups of dosed rats and mice. Survival was significantly shortened in the high-dose female rats and in the low- and mid-dose female mice.

In male and female rats, hepatocellular carcinomas or neoplastic nodules occurred at incidences that were dose-related, and the incidences in all dosed groups (except low-dose females) were higher than those in the controls. The occurrence of follicular-cell adenomas or carcinomas of the thyroid was dose-related. Among groups of male and female rats, the incidences in the mid- and high-dose groups of either sex were significantly higher than those of the corresponding controls.

In male and female mice, adenomas in the harderian glands occurred in all dosed groups at incidences that were significantly higher than the incidence in the matched controls.

In low-dose male mice and in high-dose female mice, hepatocellular adenomas or carcinomas occurred at incidences significantly higher than those in the matched controls.

In female mice, follicular-cell adenomas in the thyroid occurred with a positive linear trend, and in a direct comparison the incidence in the high-dose group was also significantly higher than that in the controls.

Tumors occurring among male mice at increased incidences which could not be statistically related to the chemical were adenomas in the pituitary and hemangiomas of the circulatory system.

Under the conditions of this bioassay, 4,4'-oxydianiline was carcinogenic for male and female F344 rats, inducing hepatocellular carcinomas or neoplastic nodules and follicular-cell adenomas or carcinomas of the thyroid. 4,4'-Oxydianiline was also carcinogenic for male and female B6C3F$_1$ mice, including adenomas in the harderian glands, hepatocellular adenomas or carcinomas in both sexes, and follicular-cell adenomas in the thyroid of females.

Report Date: August 1980

Levels of Evidence of Carcinogenicity:

Male Rats:	Positive
Female Rats:	Positive
Male Mice:	Positive
Female Mice:	Positive

TR-206 Carcinogenesis Bioassay of 1,2-Dibromo-3-chloropropane (CAS No. 96-12-8) in F344 Rats and B6C3F$_1$ Mice (Inhalation Study)

1,2-Dibromo-3-chloropropane (DBCP), a contaminant (0.05%) of the flame retardant tris(2,3-dibromopropyl)-phosphate, has been used primarily as a soil fumigant to control nematodes. Unlike other halogenated nematocides, DBCP can be applied to soil without damaging growing perennials. Since it is slightly soluble in water at the concentrations used (30 ppm), DBCP can be either injected directly into the soil or added to irrigation water. By 1972, an estimated 12.3 million pounds were being used annually; in 1977, a total of 832,000 pounds were used in California, mostly on grapes and tomatoes.

A carcinogenesis bioassay of technical grade 1,2-dibromo-3-chloropropane (DBCP), which contained trace amounts of epichlorohydrin and 1,2-dibromoethane, was conducted by exposing groups of 50 F344 rats and B6C3F$_1$ mice of each sex by inhalation to concentrations of 0.6 or 3.0 ppm DBCP for 6 hours per day, 5 days per week, for 76 to 103 weeks. Untreated chamber controls consisted of 50 rats and 50 mice of each sex. Surviving high-dose rats were killed at week 84. Surviving high-dose female mice and low- and high-dose male mice were killed at week 76. Low-dose rats and female mice were killed at week 104.

Accelerated mortality occurred in the high-dose groups of both species. Early deaths of high-dose rats and mice were associated with respiratory tract tumors. Interference with breathing and metastasis to the brain were major contributing factors in these deaths. Among male mice, accelerated mortality occurred in low-dose and control groups as well as in the high-dose group. Urogenital infection appeared to be associated with these deaths.

Carcinomas, squamous-cell carcinomas, and adenocarcinomas of the nasal cavity and squamous-cell papillomas of the tongue each occurred in high-dose male rats at incidences significantly higher than those in the corresponding controls. Adenocarcinomas, adenomas, adenomatous polyps, and squamous-cell papillomas of the nasal cavity and adenomatous polyps of the nasal turbinates occurred in low-dose male rats with significantly increased incidences relative to controls.

Carcinomas and adenocarcinomas of the nasal cavity, squamous-cell papillomas of the tongue, squamous-cell papillomas and carcinomas (combined) of the pharynx, and adenomas of the adrenal cortex each occurred in high-dose female rats at incidences significantly higher than those in the corresponding controls. Also, adenomas and squamous-cell papillomas of the nasal cavity, adenomas of the adrenal cortex, and fibroadenomas of the mammary gland were increased significantly in low-dose female rats when compared with controls.

Adenocarcinomas of the nasal cavity in high-dose female mice, papillary carcinomas in low-dose female

mice, and carcinomas, squamous cell carcinomas of the nasal cavity, and alveolar/bronchiolar adenomas or carcinomas of the lung in high-dose male and female mice occurred at incidences significantly higher than those in the corresponding controls.

Exposure to DBCP vapor was also associated with toxic tubular nephropathy in rats and mice of either sex and with proliferative changes in the nasal mucosa, lung, and forestomach in mice.

Under the conditions of this bioassay, DBCP was carcinogenic for male and female F344/N rats, including increased incidences of nasal cavity tumors and tumors of the tongue in both sexes, and cortical adenomas in the adrenal glands of females. DBCP was carcinogenic in male and female $B6C3F_1$ mice, including increased incidences of nasal cavity tumors and lung tumors.

Synonyms: DBCP; dibromochloropropane; Nemagon; Fumazone

Report Date: March 1982

Note: 1,2-Dibromo-3-chloropropane was previously tested in Osborne-Mendel rats and $B6C3F_1$ mice by gavage (See TR-28, reported 1978).

TR-207 Carcinogenesis Bioassay of Cytembena (CAS No. 21739-91-3)

A carcinogenesis bioassay of cytembena, a cytostatic agent, was conducted by injecting intraperitoneally 7 or 14 mg/kg into groups of 50 male and 50 female F344 rats and 12 or 24 mg/kg into groups of 50 male or 50 female $B6C3F_1$ mice three times per week for 104 weeks. Groups of 50 rats and 50 mice of both sexes served as vehicle controls.

Mean body weights of dosed and vehicle-control rats were comparable throughout the bioassay. Mean body weights of dosed and vehicle-control mice were comparable for the first 73 weeks of the bioassay; mean body weight of the high dose male mice was slightly lower than that of the vehicle controls after 73 weeks, and that of the high-dose female mice was lower after week 87.

In dosed male rats, mesotheliomas in the tunica vaginalis and malignant mesotheliomas in multiple organs occurred with dose-related trends and at incidences in each of the dosed groups which were significantly higher than those in the vehicle control rats.

In dosed female rats, fibroadenomas in the mammary gland occurred with a dose-related trend and at a significantly higher incidence in the high-dose group than in vehicle control rats.

Under the conditions of this bioassay, cytembena was carcinogenic for male and female F344 rats, causing increased incidences of mesotheliomas in the tunica vaginalis and in multiple organs of males and fibroadenomas in the mammary gland of females. Cytembena was not carcinogenic for male or female $B6C3F_1$ mice.

Synonyms: cytembene; 2-butenoic acid; 3-bromo-4-(4-methoxyphenyl)-4-oxo-, sodium salt

Report Date: May 1981

TR-208 Carcinogenesis Bioassay of FD & C Yellow No. 6 (CAS No. 2783-94-0)

A carcinogenesis bioassay was conducted using groups of 50 male and 50 female F344 rats and $B6C3F_1$ mice which were fed diets containing 12,500 or 25,000 ppm FD & C Yellow No. 6, a widely used food colorant, for 103 weeks. Groups of 90 male and 90 female rats and 50 male and 50 female mice served as undosed controls.

Throughout the study, mean body weights of high-dose female rats and all low-dose groups were comparable with those of the controls, but mean body weights of high-dose male rats and high-dose male and female mice were slightly lower (10% or less) than those of the controls.

No compound-related neoplastic or nonneoplastic lesions were observed in the rats.

The incidence of hepatocellular carcinomas in low-dose male mice was significantly higher than that in the controls, but the lack of a significant increase in high-dose males and the variability of liver tumors in $B6C3F_1$ male mice precluded clearly relating the occurrence of these tumors to the administration of FD & C Yellow No. 6.

Under the conditions of this bioassay, there was no clear evidence of the carcinogenicity of FD & C Yellow No. 6 in F344 rats or $B6C3F_1$ mice of either sex.

Synonym: Sunset Yellow FCF

Report Date: May 1981

TR-209 Carcinogenesis Bioassay of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (CAS No. 1746-01-6) in Osborne-Mendel Rats and $B6C3F_1$ Mice (Gavage Study)

A carcinogenesis bioassay of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), a contaminant in several phenoxy herbicides, was conducted by administering TCDD by gavage to Osborne-Mendel rats and $B6C3F_1$ mice for 104 weeks.

Fifty rats and mice of each sex were given TCDD suspended in a vehicle of 9:1 corn oil-acetone 2 days per week for 104 weeks at doses of 0.01, 0.05, or 0.5 μg/kg/wk for rats and male mice and 0.04, 0.2, or 2.0 μg/kg/wk for female mice. Seventy-five rats and 75 mice of each sex served as vehicle controls. One untreated control group containing 25 rats and 25 mice of each sex was present in the TCDD treatment room, and one untreated control group containing 25 rats and 25 mice of each sex was present in the vehicle-control room. All surviving animals were killed at 105 to 108 weeks.

In rats, a dose-related depression in mean body weight gain was observed in the males after week 55 of the bioassay and in the females after week 45. In mice, the mean body weight gain in the dosed groups was comparable to that of the vehicle-control groups.

In male rats, increased incidences of follicular-cell adenomas in the thyroid were dose related and were significantly (P = 0.001) higher in the high-dose group than in the vehicle controls (1/69, 1%; 5/48, 10%; 6/50, 12%; 10/50, 20%). Similarly in the female rats, an increase (though not statistically significant) was seen in the high-dose group (3/73, 4%; 2/45, 4%; 1/49, 2%; 6/47, 13%).

In female rats, the incidence of neoplastic nodules of the liver in the high-dose group was significantly (P = 0.006) higher than that in the vehicle control group (5/75, 7%; 1/49, 2%; 3/50, 6%; 12/49, 24%).

In male and female mice, incidences of hepatocellular carcinomas were dose related and the incidences in the high-dose groups were significantly (P = 0.002 and 0.014, respectively) higher than those in the corresponding vehicle control groups (males: 8/73, 11%; 9/49, 18%; 9/49, 16%; 17/50, 34%; females: 1/73, 1%; 2/50, 4%; 2/48, 4%; 6/47, 13%).

In female mice, follicular-cell adenomas in the thyroid occurred at dose-related incidences, and were significantly (P = 0.009) higher in the high-dose groups than those in the vehicle controls (0/69, 0%; 3/50, 6%; 1/47, 2%; 5/46, 11%).

Increased incidences of toxic hepatitis related to the administration of the test chemical were detected among high-dose rats and high-dose mice of each sex.

Under the conditions of this bioassay, 2,3,7,8-tetrachlorodibenzo-p-dioxin was carcinogenic for Osborne-Mendel rats, including follicular-cell thyroid adenomas in males and neoplastic nodules of the liver in females. TCDD was also carcinogenic for B6C3F$_1$ mice, including hepatocellular carcinomas in male and females and follicular-cell thyroid adenomas in females.

Synonyms: 2,3,7,8-TCDD; TCDD

Report Date: February 1982

Note: 2,3,7,8-Tetrachlorodibenzo-p-dioxin was previously tested in Swiss-Webster mice administered dermally (See TR-201, reported 1982).

TR-210 Carcinogenesis Bioassay of 1,2-Dibromoethane (CAS No. 106-93-4) in F344 Rats and B6C3F$_1$ Mice (Inhalation Study)

A carcinogenesis bioassay of 1,2-dibromoethane, a widely used nematocide and leaded gasoline additive, was conducted by exposing groups of 50 F344 rats and B6C3F$_1$ mice of each sex by inhalation to concentrations of 10 or 40 ppm of the 1,2-dibromoethane for 78-103 weeks. Untreated controls consisted of 50 rats and 50 mice of each sex exposed in chambers to ambient air.

Throughout the study, mean body weights of high-dose rats and high-dose mice of either sex were lower than those of the corresponding untreated controls. Survival of the high-dose rats of either sex and of the low- and high-dose female mice was significantly shorter than that in the corresponding controls.

The principal cause of early death in control and dosed male mice was ascending, suppurative urinary tract infection that resulted in necrotic, ulcerative lesions around the urethral opening, chronic or suppurative cystitis (often with urinary tract obstruction), and ascending suppurative pyelonephritis.

Carcinomas and adenocarcinomas of the nasal cavity were observed with significantly increased incidences (P<0.001) in high-dose rats of either sex relative to controls. The incidences of adenocarcinomas and adenomas of the nasal cavity were also significantly increased (P<0.001) in low-dose rats of either sex. Adenomatous polyps of the nasal cavity showed significantly increased incidence (P<0.001) in low-dose male rats. The combined incidence of alveolar/bronchiolar adenomas and carcinomas was statistically significant (P = 0.024) for high-dose female rats.

Hemangiosarcomas of the circulatory system (mainly spleen) and mesotheliomas of the tunica vaginalis occurred in high-dose male rats with significantly increased incidences (P<0.001) relative to controls.

The incidence of fibroadenomas of the mammary gland was significantly elevated (P<0.001) in dosed female rats relative to controls.

The incidences of alveolar/bronchiolar carcinoma and alveolar/bronchiolar adenoma were significantly increased (P<0.001) in high-dose male mice relative to controls. These tumors were also increased in high-dose female mice (P = 0.007 for adenomas and P<0.001 for carcinomas).

Hemangiosarcomas occurred in low- and high dose female mice at incidences significantly greater (P<0.001) than the incidence in the controls (0/50). High-dose female mice also had significantly increased incidences of subcutaneous fibrosarcomas (P<0.001) and of nasal cavity carcinomas (P = 0.013). Low-dose female mice also showed a significantly increased incidence (P<0.001) of mammary gland adenocarcinomas.

Exposure to 1,2-dibromoethane was also associated with hepatic necrosis and toxic nephropathy in rats of either sex, testicular degeneration in male rats, retinal degeneration in female rats, and epithelial hyperplasia of the respiratory system in mice.

Under the conditions of this bioassay, 1,2-dibromoethane was carcinogenic for F344 rats, causing increased incidences of carcinomas, adenocarcinomas, adenomas of the nasal cavity, and hemangiosarcomas of the circulatory system in males and females; mesotheliomas of the tunica vaginalis and adenomatous polyps of the nasal cavity in males; and fibroadenomas of the mammary gland and alveolar/bronchiolar adenomas and carcinomas (combined) in females. 1,2-Dibromoethane was carcinogenic for B6C3F$_1$ mice, causing alveolar/bronchiolar carcinomas and alveolar/bronchiolar adenomas in males and females; and hemangiosarcomas of the circulatory system, fibrosarcomas in the sub-

cutaneous tissue, carcinomas of the nasal cavity, and adenocarcinomas of the mammary gland in females.

Synonyms: ethylene dibromide; EDB; ethylene bromide

Report Date: March 1982

Note: 1,2-Dibromoethane was previously tested in Osborne-Mendel rats and B6C3F$_1$ mice by gavage (See TR-86, reported 1978).

TR-211 Carcinogenesis Studies of C.I. Acid Orange 10 (CAS No. 1936-15-8) in F344 Rats and B6C3F$_1$ Mice (Feed Studies)

Carcinogenesis studies of 80% pure C.I. Acid Orange 10 (a monoazo textile dye) were conducted by feeding to groups of 50 male and 50 female F344/N rats diets containing 1,000 or 3,000 ppm C.I. Acid Orange 10 for 103 weeks. Groups of 50 male and 50 female B6C3F$_1$ mice were fed diets containing 3,000 or 6,000 ppm for 103 weeks. Groups of 90 male and 90 female untreated rats and 50 male and 50 female untreated mice served as controls.

Mean body weights and clinical signs of control and dosed rats and mice were comparable. Because no toxic effects or consistent weight differences were observed, the rats and mice may have been able to tolerate higher doses.

In male rats with neoplastic nodules of the liver, the dose response trend was positive ($P<0.05$) and the incidence in the 3,000 ppm group was increased ($P<0.05$) compared to controls (control, 5/90, 6%; low dose, 3/50, 6%; high dose, 8/50, 16%). One male rat in the high dose group had both a neoplastic nodule and a carcinoma of the liver. This marginal increase in liver cell neoplasms may have been associated with the dietary administration of C.I. Acid Orange 10.

For both dose groups of male and female rats, leukemia was significantly ($P<0.05$) decreased in a dose related ($P<0.005$) trend (male: 22/90, 24%; 4/50, 8%; 3/50, 6%; female: 16/88, 18%; 2/50, 4%; 0/50).

No compound-related nonneoplastic or neoplastic lesions were observed in the female rats or in mice of either sex.

For 103 weeks C.I. Acid Orange 10 was given in the diets of male and female F344/N rats (0, 0.1, or 0.3%) and of male and female B6C3F$_1$ mice (0, 0.3%, or 0.6%). Under these conditions, there was no evidence of carcinogenicity for male and female F344/N rats or for male and female B6C3F$_1$ mice.

Synonym: 7-hydroxy-8-(phenylazo)-1,3-naphthalenedisulfonic acid, disodium salt

Report Date: October 1987

TR-212 Carcinogenesis Bioassay of Di(2-ethylhexyl)adipate (CAS No. 103-23-1) in F344 Rats and B6C3F$_1$ Mice (Feed Study)

Di(2-ethylhexyl)adipate is a plasticizer used to give flexibility to vinyl plastics. A carcinogenesis bioassay was conducted by feeding diets containing 12,000 or 25,000 ppm of di(2-ethylhexyl)adipate to groups of 50 male and 50 female F344 rats and 50 male and 50 female B6C3F$_1$ mice for 103 weeks. Groups of 50 undosed rats and mice of each sex served as controls. All surviving animals were killed at 104 to 107 weeks.

Mean body weights of high-dose rats and mice of either sex were lower than those of the controls throughout the study.

Compound administration was not associated with tumor formation in F344 rats of either sex.

Hepatocellular carcinomas or adenomas occurred in mice of both sexes in a dose-related fashion at incidences that were significantly higher for high-dose males and for low- and high-dose females than those in the controls. When compared with the incidence in historical laboratory control mice, however, the liver tumors in male mice could not be clearly related to compound administration.

Under the conditions of this bioassay, di(2-ethylhexyl)adipate was not carcinogenic for F344 rats. Di(2-ethylhexyl)adipate was carcinogenic for female B6C3F$_1$ mice, causing increased incidences of hepatocellular carcinomas, and was probably carcinogenic for male B6C3F$_1$ mice, causing hepatocellular adenomas.

Synonyms: bis(2-ethylhexyl)adipate; DEHA; octyl adipate; diocytl adipate; DOA

Report Date: March 1982

TR-213 Carcinogenesis Bioassay of Butyl Benzyl Phthalate (CAS No. 85-68-7) in F344/N Rats and B6C3F$_1$ Mice (Feed Study)

A carcinogenesis bioassay of butyl benzyl phthalate, a plasticizer for vinyl chloride plastics, was accomplished by feeding diets containing 6,000 or 12,000 ppm of the phthalate to groups of 50 F344/N rats and 50 B6C3F$_1$ mice of each sex for 28 to 103 weeks.

Mean body weights of dosed female rats and mice of each sex were lower than those of the control animals throughout most of the study.

After week 14, an increasing number of dosed male rats died as a result of an unexplained internal hemorrhaging, and all surviving male rats were killed at week 29 to 30. Because of compound-related mortality, butyl benzyl phthalate was not adequately tested for carcinogenicity in male F344/N rats.

Mononuclear cell leukemias occurred at a statistically significant ($P=0.011$) increased incidence in the high-

dose group of female rats when compared with the control group and with a significantly (P = 0.006) increasing trend (controls 7/49, 14%; low-dose 7/49, 14%; high-dose 18/50, 36%). The incidence in the high-dose group and the overall trend remained statistically significant (P = 0.008 and P = 0.019) when compared with the historical incidence for F344/N female rats with leukemia at this laboratory (77/ 399, 19%). Further, this leukoproliferation was generally characterized by splenomegaly and often by hepatomegaly.

Administration of butyl benzyl phthalate was not associated with increased incidences of any type of tumor among male or female mice.

Tumor rates were decreased in female rats for fibroadenomas of the mammary glands (20/49, 14/49, 9/50) and in male mice for lymphomas of the hematopoietic system (13/50, 11/49, 4/50) and for alveolar/bronchiolar adenomas or carcinomas (17/50, 11/49, 8/50).

Under the conditions of this bioassay, butyl benzyl phthalate was probably carcinogenic for female F344/N rats, causing an increased incidence of mononuclear cell leukemias. The male F344/N rat study was considered inadequate for evaluation due to compound-related toxicity and early mortality. Butyl benzyl phthalate was not carcinogenic for $B6C3F_1$ mice of either sex.

Synonyms: BBP; benzyl butyl phthalate; phthalic acid; benzyl butyl ester; Santicizer 160

Report Date: August 1982

TR-214 Carcinogenesis Bioassay of Caprolactam (CAS No. 105-60-2) in F344 Rats and $B6C3F_1$ Mice (Feed Study)

A carcinogenesis bioassay of caprolactam, a chemical intermediate used in the production of nylon 6, was conducted by feeding diets containing 3,750 or 7,500 ppm caprolactam to groups of 50 male or female F344 rats and 7,500 or 15,000 ppm to groups of 50 male or female $B6C3F_1$ mice for 103 weeks. Control groups consisted of 50 undosed rats and 50 undosed mice of each sex.

Throughout the bioassay, mean body weight gains for dosed rats and mice of either sex were decreased when compared with those of the controls. No other compound-related effects were observed.

Under the conditions of this bioassay, caprolactam was not carcinogenic for F344 rats or $B6C3F_1$ mice.

Synonyms: aminocaproic lactam; 2-oxohexamethylenimine

Report Date: March 1982

TR-215 Carcinogenesis Bioassay of Bisphenol A (CAS No. 80-05-7) in F344 Rats and $B6C3F_1$ Mice (Feed Study)

A carcinogenesis bioassay of bisphenol A, an intermediate used in the manufacture of epoxy, polycarbonate, and polyester-styrene resins, was conducted by feeding diets containing 1,000 or 2,000 ppm of the test chemical to groups of 50 F344 rats of either sex, 1,000 or 5,000 ppm to groups of 50 male $B6C3F_1$ mice, and 5,000 or 10,000 ppm to groups of 50 female $B6C3F_1$ mice for 103 weeks. Groups of 50 rats and 50 mice of either sex served as controls.

Mean body weights of rats of either sex and of high- and low-dose female mice and high-dose male mice were lower than those of the controls throughout the study. Since food consumption of dosed female rats was only 70% to 80% that of the controls throughout most of this study, reduced body weight gain was probably due to reduced food consumption. Food consumption by dosed male rats was 90% that of controls. Food consumption among all groups of mice appear to be similar.

Leukemias occurred at increased incidences in dosed rats of both sexes. In male rats, the dose-related (13/50, 12/50, 23/50) trend was statistically significant (P = 0.021) by a Cochran-Armitage test, but neither the trend nor the increase in the high-dose group was significant by life table analyses, which adjust for survival differences among groups. The increased incidences in dosed female rats were also not statistically significant (7/50, 13/50, 12/50).

Interstitial-cell tumors of the testes occurred at statistically significant incidences in low- and high-dose male rats; however, since this lesion normally occurs at a high incidence in aging F344 male rats, the increased incidence observed in this study was not considered compound related (35/49, 48/50, 46/49).

In male mice, there was an increased incidence of leukemias or lymphomas (2/49, 9/50, 5/50), but this increase was not statistically significant.

A compound-related increased incidence of multinucleated giant hepatocytes was observed in male mice (1/49, 41/49, 41/50), but there was no increase of liver tumors in male mice.

The marginally significant increase in leukemias in male rats, along with an increase (not statistically significant) in leukemias in female rats and a marginally significant increase in the combined incidence of lymphomas and leukemias in male mice, suggests that exposure to bisphenol A may be associated with increased cancers of the hematopoietic system. A statistically significant increase in interstitial-cell tumors of the testes in male rats was also suggestive of carcinogenesis, but was not considered to be convincing evidence of a compound-related effect because this lesion normally occurs at a high incidence in aging F344 rats.

Under the conditions of this bioassay, there was no convincing evidence that bisphenol A was carcinogenic for F344 rats or $B6C3F_1$ mice of either sex.

Synonym: 4,4'-isopropylidenediphenol

Report Date: March 1982

TR-216 Carcinogenesis Bioassay of 11-Aminoundecanoic Acid (CAS No. 2432-99-7) in F344 Rats and B6C3F$_1$ Mice

11-Aminoundecanoic acid is the monomer used in the manufacture of the polyamide, nylon-11. Aminoundecanoic acid is synthesized through a series of reactions from ricinoleic acid isolated from castor bean oil.

Nylon-11 is used in automobile parts, industrial fabrics (e.g. filter bags, work clothes, and netting), and brushes because of its resistance to vibration and shock and its stability when in contact with fuels. Nylon-11 resins are approved by the U.S. Food and Drug Administration for use on food contact films.

A carcinogenesis bioassay of 11-aminoundecanoic acid was carried out by administering diets containing 7,500 or 15,000 ppm of 11-aminoundecanoic acid to F344 rats and B6C3F$_1$ mice. Groups of 50 rats and 50 mice of either sex were administered the test chemical for 104 weeks (rats) or 103 weeks (mice). Controls consisted of 50 untreated rats and 50 untreated mice of each sex.

Nonneoplastic effects included dose-related decreases in mean body weight gain and survival for male rats and for mice of each sex; a dose-related increased incidence of hyperplasia of the transitional epithelium of the kidney and urinary bladder in rats of each sex; and mineralization of the kidney in dosed mice of each sex.

Neoplastic nodules of the liver in dosed male rats (control 1/50, 2%; low dose 9/50, 18%; high dose 8/50, 16%; $P<0.01$) and transitional-cell carcinomas of the urinary bladder in high-dose male rats (control 0/48, 0%; low dose 0/48, 0%; high dose 7/49, 14%: $P<0.01$) were observed at significantly increased incidences compared with controls. Malignant lymphomas occurred at a significantly ($P<0.05$) increased rate in low-dose male mice (control 2/50, 4%; low dose 9/50, 18%; high dose 4/50, 8%).

Under the conditions of this bioassay, 11-aminoundecanoic acid was carcinogenic for male F344 rats, inducing neoplastic nodules in the liver and transitional-cell carcinomas in the urinary bladder. The test chemical was not carcinogenic for female F344 rats. No clear evidence was found for the carcinogenicity of 11-aminoundecanoic acid in B6C3F$_1$ mice of either sex, although the increase in malignant lymphoma in male mice may have been associated with administration of 11-aminoundecanoic acid.

Report Date: May 1982

TR-217 Carcinogenesis Bioassay of Di(2-ethylhexyl)phthalate (CAS No. 117-81-7) in F344 Rats and B6C3F$_1$ Mice (Feed Studies)

A bioassay of di(2-ethylhexyl)phthalate, the most commonly used plasticizer for polyvinylchloride polymers, for possible carcinogenicity was conducted by feeding diets containing 6,000 or 12,000 ppm of the test chemical to groups of 50 male and 50 female F344 rats and 3,000 or 6,000 ppm to groups of 50 male and 50 female B6C3F$_1$ mice for 103 weeks. Controls consisted of 50 untreated rats and 50 untreated mice of either sex.

Mean body weights of dosed male rats (high- and low-dose), high-dose female rats, and dosed female mice (high- and low-dose) were marginally-to-moderately lower than those of the corresponding controls at the end of the chronic study, reflecting a decrease in body weight gain. Food consumption was reduced slightly in rats of either sex, whereas there was no apparent difference among the mouse groups.

Female rats and male and female mice administered di(2-ethylhexyl)phthalate had significantly higher incidences of hepatocellular carcinomas than those observed in the controls (rats – males: 1/50, 2%; 1/49, 2%; 5/49, 10%; females – 0/50, 0%; 2/49, 4%; 8/50, 16%, $P=0.003$; mice – males: 9/50, 18%; 14/48, 29%; 19/50, 38%, $P=0.022$; females: 0/50, 0%; 7/50, 14%; $P=0.006$, 17/50, 34%, $P<0.001$). Further, a statistically significant positive trend for hepatocellular carcinomas occurred in female rats ($P=0.002$) and in male ($P=0.018$) and female ($P<0.001$) mice.

In addition, di(2-ethylhexyl)phthalate caused a statistically significant increased incidence of male rats with either hepatocellular carcinomas or neoplastic nodules (3/50, 6%; 6/49, 12%; 12/49, 24%; $P=0.010$).

Degeneration of the seminiferous tubules was observed in the high-dose male rats (1/49, 2%; 2/44, 5%; 43/48, 90%) and in the high-dose male mice (1/49, 2%; 2/48 4%; 7/49, 14%). Hypertrophy of cells in the anterior pituitary was also found at increased incidences in the high-dose male rats (1/46, 2%; 0/43, 0%; 22/49, 45%).

Under the conditions of this bioassay, di(2-ethylhexyl)phthalate was carcinogenic for F344 rats and B6C3F$_1$ mice, causing increased incidences of female rats and male and female mice with hepatocellular carcinomas, and inducing an increased incidence of male rats with either hepatocellular carcinomas or neoplastic nodules.

Synonym: DEHP

Report Date: March 1982

TR-218 Monitoring Guidelines for the Conduct of Carcinogen Bioassays

Note to the Reader: This document was prepared as a result of a discussion group on quality assurance conducted at the National Cancer Institute in 1979.

Report Date: 1981

TR-219 Carcinogenesis Bioassay of 2,6-Dichloro-p-Phenylenediamine (CAS No. 609-20-1) in F344 Rats and B6C3F$_1$ Mice (Feed Study)

A carcinogenesis bioassay of 2,6-dichloro-p-phenylenediamine, a chemical intermediate, was conducted in groups of 50 F344 rats and B6C3F$_1$ mice of either sex. Male rats were fed diets containing 1,000 or 2,000 ppm 2,6-dichloro-p-phenylenediamine and female rats were fed 2,000 or 6,000 ppm for 103 weeks. Mice were fed 1,000 or 3,000 ppm of the test chemical for 103 weeks and observed for an additional 8 weeks. Controls consisted of 50 untreated rats and 50 untreated mice of each sex.

Throughout the study, mean body weights of dosed rats and mice of either sex were lower than those of the corresponding controls. A dose-related weight gain depression was particularly pronounced for rats.

Ectopic hepatocytes were observed at an increased incidence in the pancreas and nephrosis was observed in increased severity in dosed rats of either sex when compared with the corresponding controls. No increase in any tumor type was observed in treated male or female rats when compared to controls.

Increased incidences of liver tumors were observed in mice of both sexes. In male mice, the incidence of hepatocellular adenomas exhibited a significant positive dose-related trend ($P = 0.002$), and the increased incidence of hepatocellular adenomas was statistically significant in the high-dose group (4/50, 7/50, 15/50: $P = 0.005$). The combined incidence of hepatocellular adenomas and carcinomas showed a significant positive dose-related trend ($P = 0.004$) and was statistically significant in the high-dose group (16/50, 19/50, 29/50: $P = 0.008$).

In female mice, hepatocellular carcinomas exhibited a significant positive dose-related trend ($P = 0.025$), but no single dose group had a statistically significant increased incidence of either adenomas (4/50, 4/50, 9/50; high-dose effect: $P = 0.12$) or carcinomas (2/50, 2/50, 7/50; high-dose effect: $P = 0.08$) alone. When the incidences of hepatocellular adenomas and carcinomas were combined (6/50, 6/50, 16/50), these data gave a positive dose-related trend ($P = 0.004$) and were statistically significant in the high-dose group ($P = 0.014$).

Under the conditions of this bioassay, 2,6-dichloro-p-phenylenediamine was carcinogenic for male and female B6C3F$_1$ mice, causing increased incidences of combined hepatocellular adenomas and carcinomas, and for male B6C3F$_1$ mice, causing an increased incidence of hepatocellular adenomas alone. 2,6-Dichloro-p-phenylenediamine was not carcinogenic for male or female F344 rats.

Report Date: March 1982

TR-220 Carcinogenesis Bioassay of C.I. Acid Red 14 (CAS No. 3567-69-9) in F344/N Rats and B6C3F$_1$ Mice (Feed Study)

A carcinogenesis bioassay of textile grade C.I. Acid Red 14 (67%-71% purity) was conducted by feeding diets containing 6,000 or 12,500 ppm of this dye for 103-104 weeks to groups of 50 male F344 rats, 12,500 or 25,000 ppm to groups of 50 female F344 rats, and 3,000 or 6,000 ppm to groups of 50 B6C3F$_1$ mice of either sex. Groups of 90 untreated rats of either sex and 50 untreated mice of either sex served as controls.

Throughout the study, mean body weights of dosed rats of either sex and dosed female mice were comparable with those of the controls, while the mean body weight of high-dose male mice was slightly lower than that of the controls.

Fourteen male rats in the low-dose group and 2 in the high-dose group accidentally drowned between weeks 84 and 103; 56% and 60% of these groups survived to terminal kill compared with 78% of the controls. These losses may have reduced the sensitivity of the assay in male rats.

Rats and mice may have tolerated higher doses, but the slight depression of mean body weight in high-dose male mice and the non-neoplastic lesions observed in dosed female mice and in rats of both sexes suggest that doses administered in this study could be considered maximum tolerated doses.

Endometrial stromal polyps of the uterus were observed in high-dose female rats at an incidence significantly higher ($P = 0.008$) than that seen in the controls (controls: 9/87, 10%; low-dose: 11/50, 22%; high-dose: 14/50, 28%). However, the observed incidence of this tumor in the dosed groups was similar to the historical rate in untreated female F344 rats at this laboratory (65/286, 23%; range 10%-37%). Hence, the increased incidence of this lesion is not regarded as being associated with the administration of C.I. Acid Red 14.

Administration of C.I. Acid Red 14 to mice was not associated with an increased incidence of any tumor type.

Under the conditions of this bioassay, C.I. Acid Red 14 was not carcinogenic for F344 rats or B6C3F$_1$ mice of either sex.

Synonym: 4-hydroxy-3-(4-Sulfo-1-naphthalenyl)azo-1-naphthalenesulfonic acid, disodium

Report Date: March 1982

TR-221 Carcinogenesis Bioassay of Locust Bean Gum (CAS No. 9000-40-2) in F344 Rats and B6C3F$_1$ Mice (Feed Study)

A carcinogenesis bioassay of locust bean gum, a widely used food stabilizer, was conducted by feeding diets containing 25,000 or 50,000 ppm of the test substance to

50 F344 rats and 50 B6C3F$_1$ mice of either sex for 103 weeks. Groups of 50 untreated rats and mice of either sex served as controls.

Mean body weights of high- and low-dose rats of either sex, of low-dose male mice, and of high- and low-dose female mice were comparable with those of the controls; mean body weights of high-dose male mice were slightly lower than those of controls. No other compound-related clinical signs or effects on survival were observed. Although the rats and mice might have been able to tolerate higher doses, 50,000 ppm (5%) is the recommended maximum concentration of a test chemical mixed in feed according to the guidelines of the Bioassay Program.

Although alveolar/bronchiolar adenomas occurred in low-dose male mice at a significantly ($P = 0.017$) higher incidence than that in the controls (7/50, 17/50, 11/50), no significant statistical results were obtained when the combined incidence of animals with either alveolar/bronchiolar adenomas or carcinomas was analyzed (14/50, 21/50, 14/50). Cortical adenomas in the adrenal gland of female rats occurred with a statistically significant ($P = 0.042$) positive trend (1/50, 4/50, 6/50), but comparisons between test groups and the control group were not statistically different.

Under the conditions of this bioassay, locust bean gum was not carcinogenic for male or female F344 rats or B6C3F$_1$ mice.

Report Date: February 1982

TR-222 Carcinogenesis Bioassay of Disperse Yellow 3 (CAS No. 2832-40-8) in F344 Rats and B6C3F$_1$ Mice (Feed Study)

A carcinogenesis bioassay of C.I. Disperse Yellow 3 (87.6% dye), a textile dye, was conducted by feeding diets containing 5,000 or 10,000 ppm of the test substance to groups of 50 F344 rats of either sex for 103 weeks. Similar groups of 50 B6C3F$_1$ mice received diets containing 2,500 or 5,000 ppm of the test substance for 103 weeks. Groups of 50 untreated rats and mice of each sex served as controls.

Throughout the bioassay, mean body weights of dosed rats and mice of either sex were lower than those of the controls. Survival of dosed rats of either sex was significantly greater than that of the corresponding controls. No other compound-related clinical signs or effects on survival were observed.

A significant increase in neoplastic nodules of the liver occurred in dosed male rats as compared to controls (controls 1/49, 2%; low-dose 15/50, 30%; $P<0.001$; high-dose, 10/50, 20%; $P<0.01$). No increase was observed for female rats.

Stomach tumors, rare in F344 rats (10/2960, 0.3%), were found in the dosed male rats: one adenocarcinoma and a sarcoma in a high-dose male and in the low-dose group a squamous cell papilloma, fibrosarcoma, adenoma, and mucinous adenocarcinoma. The incidence of these tumors was not significantly greater than that in controls; thus, the association between the administration of C.I. Disperse Yellow 3 and the stomach tumors in male rats is not clearly established.

Negative trends in the incidences of certain primary tumors in dosed rats included: decreased lymphocytic leukemia in both sexes; decreased malignant mesothelioma and C-cell carcinoma of the thyroid in males; and decreased pituitary chromophobe adenoma and endometrial stromal polyps in females.

Hepatocellular adenomas occurred in dosed female mice at incidences significantly higher than that in the controls (control 0/50, 0%; low-dose 6/50, 12%, $P<0.05$; high-dose 12/50, 24%, $P<0.001$). The incidences of hepatocellular carcinomas were also higher in the dosed female mice than in the controls, but the increased incidences were not statistically significant (2/50, 4/50, 5/50). A significantly ($P<0.05$) lower incidence of hepatocellular adenomas was detected among low-dose (7/50, 1/49, 7/49) male mice.

Alveolar/bronchiolar adenomas occurred in high-dose male mice at an incidence significantly ($P<0.05$) higher than that in the controls (control 2/50, 4%; low-dose 6/49, 12%; high-dose 9/49, 18%). However, the high-dose effect was not significant when adenomas and carcinomas were combined; the incidence among low-dose female mice was significantly reduced as compared with controls. Thus, the incidence of alveolar/bronchiolar adenomas among males is not considered to be related to treatment with C.I. Disperse Yellow 3.

Malignant lymphomas occurred in a dose-related ($P<0.05$) trend in female mice and at incidences greater ($P<0.05$) in the high-dose group than that in the controls (10/50; 16/50; 19/50). However, because of the range of variability in the historical incidence of this tumor and because of the lack of a similar effect in male mice or in male and female rats, this increase was not regarded as being unequivocally related to the administration of C.I. Disperse Yellow 3.

Under the conditions of this bioassay, C.I. Disperse Yellow 3 was considered to be carcinogenic for male F344 rats, causing an increased incidence of neoplastic nodules of the liver; this dye was not carcinogenic for female F344 rats. In addition, the stomach tumors found in the male rats may have been induced by the administration of the test chemical. C.I. Disperse Yellow 3 was carcinogenic for female B6C3F$_1$ mice, as evidenced by the increased incidence of hepatocellular adenomas; C.I. Disperse Yellow 3 was not carcinogenic for male B6C3F$_1$ mice. Also, the increased incidence of malignant lymphoma in female mice may have been associated with the administration of C.I. Disperse Yellow 3.

Synonyms: Disperse Fast Yellow 6; Acetamine Yellow CG

Report Date: May 1982

TR-223 Carcinogenesis Studies of Eugenol (CAS No. 97-53-0) in F344/N Rats and B6C3F$_1$ Mice (Feed Studies)

Carcinogenesis studies of eugenol (>99% pure), a widely used flavor additive and chemical intermediate, were conducted by feeding diets containing 6,000 or 12,500 ppm of eugenol to groups of 50 female F344/N rats and by feeding diets containing 3,000 or 6,000 ppm to groups of 50 male F344/N rats and B6C3F$_1$ mice of each sex for 103 weeks. Groups of 40 rats and 50 mice of each sex served as controls. Dose levels selected for the two year studies were based on thirteen-week (91-day) studies in which dietary concentrations for the six groups ranged from 0 to 12,500 ppm. Other than a -10% difference from controls in body weights in the 12,500 ppm male rats, no chemically related gross or histopathologic effects were observed.

In the two-year studies, with the exception of the high dose female rats and female mice, final body weights of the treated groups were comparable to their respective controls. No significant differences in survival were apparent for any of the eight groups receiving eugenol and for the appropriate controls. Food consumption among groups was not different in comparison with controls — rats: males ≥97%, females ≥91%; mice: males ≥94%, females ≥90%.

There were no significant observable differences between treated and control groups of rats for either nonneoplastic (toxic) lesions or neoplasms that could be attributed to eugenol. Increases in tumor incidences were diagnosed for low dose male rats with alveolar, bronchiolar adenomas or carcinomas (combined), for C-cell adenomas of the thyroid gland in low dose female rats, and for endometrial stromal polyps of the uterus in high dose female rats. Fibroadenomas of the mammary gland were decreased in dosed groups of female rats compared with controls. None of these differences were considered to be associated with the dietary administration of eugenol.

In male mice, the low dose animals had an increased incidence ($P<0.05$) of both hepatocellular adenomas (control, 4/50; low dose, 13/50; high dose, 10/49) and hepatocellular carcinomas (10/50, 20/50, 9/49) when compared with control animals. A significant increase in hepatic neoplasms was not observed in high dose animals. No single liver tumor type was observed in female mice with a statistically significant increased incidence. When the incidences of female mice with hepatocellular adenoma or carcinoma were combined (2/50, 7/49, 9/49), there was a dose-related positive trend and the incidence of liver neoplasms in high dose animals was higher than in controls ($P<0.05$).

Eugenol was given in the diets of female F344/N rats (0, 0.6, or 1.25%) and of male F344/N rats and male and female B6C3F$_1$ mice (0, 0.3, or 0.6%) for 103 weeks. Under these experimental conditions, there was *no evidence of carcinogenicity* observed for male or female rats. For mice there was *equivocal evidence of carcinogenicity* since eugenol caused increased incidences of both carcinomas and adenomas of the liver in male mice at the 3,000 ppm dietary level and because eugenol was associated with an increase in the combined incidences of hepatocellular carcinomas or adenomas in female mice.

Synonym: 1-allyl-3-methoxy-4-hydroxybenzene

Report Date: December 1983

TR-224 Carcinogenesis Bioassay of Tara Gum (CAS No. 39300-88-4) in F344 Rats and B6C3F$_1$ Mice (Feed Study)

A carcinogenesis bioassay of tara gum, a potential stabilizer for cosmetics and foods, was conducted by feeding diets containing 25,000 or 50,000 ppm of the test substance to 50 F344 rats and 50 B6C3F$_1$ mice of either sex for 103 weeks. Groups of 50 untreated rats and mice of either sex served as controls.

In the chronic bioassay, mean body weights of dosed and control rats of either sex were comparable over the course of the study. Feed consumption by low- and high-dose male rats was 92% and 95% that of the controls, and feed consumption by low- and high-dose female rats was 87% and 79% that of the controls. Mean body weights of high-dose mice of either sex were lower than those of controls; feed consumption by dosed mice was comparable with that of controls. Although the rats and mice might have been able to tolerate higher doses, 50,000 ppm (5%) is the recommended maximum concentration of a test substance mixed in feed, according to the guidelines of the Bioassay Program.

No tumors were observed in increased incidences that were considered to be related to administration of tara gum to either species. Interstitial cell tumors of the testis in male rats were observed in a statistically significant ($P \leq 0.003$ for trend and group comparisons) positive relationship (40/48 controls; 46/46 low dose; 48/48 high dose); because these tumors are present in almost all aged F344 male rats and because of the marginal statistical significance when time-adjusted analyses are applied, these increases are not regarded as being related to tara gum administration.

A significant ($P<0.05$) negative trend was observed in the proportion of male rats with pancreatic islet cell adenoma (5/45 controls, 1/44 low dose, 0/45 high dose), of female mice with alveolar/bronchiolar adenomas (7/50, 2/49, 2/50), and of female mice with hepatocellular adenomas (9/49, 4/49, 1/50).

Under the conditions of this bioassay, tara gum was not carcinogenic for F344 rats or B6C3F$_1$ mice of either sex.

Report Date: March 1982